DIABETES

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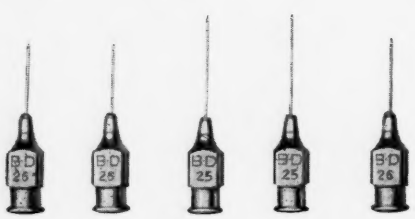

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An Abnormality of Nonesterified Fatty Acid Metabolism in Diabetes Mellitus

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The nonesterified fatty acid (NEFA) fraction of plasma, with its exceedingly rapid turnover,[1, 2] appears to be a major link in the transport of fatty acids from depots to liver and peripheral tissues.[3, 4] In normal subjects, plasma NEFA concentration falls sharply after an injection of insulin,[5] paralleling the fall of blood glucose. On the other hand, feeding of glucose or injection of glucagon causes the two components to vary in opposite directions: Blood glucose rises while NEFA falls.[5, 6] Apparently the common denominator responsible for reduction of NEFA in these two situations is an increased utilization of glucose promoted by insulin or by an input of extra glucose in the presence of adequate endogenous insulin. Diabetic subjects show an abnormally prolonged elevation of blood sugar after a glucose load and a reduced capacity to burn carbohydrate or synthesize fat.[7] The present studies indicate that control of NEFA concentration is likewise abnormal in diabetes.

Disturbances of fat metabolism have long been recognized in diabetes, and indeed continue to cause the majority of deaths.[8] Before insulin was available, ketosis, arising from incomplete combustion of fatty acids, was the main hazard. The defects of lipid metabolism in diabetes are now more chronic, but no less lethal. About half of the diabetics in one recent series[9] died from coronary occlusion, and among the entire group, the great majority showed arteriosclerosis. As further evidence of faulty fat metabolism, xanthomata and fatty liver are frequently associated with diabetes,[10] and obesity may be the forerunner of the disease.[11]

Hyperlipemia, mainly an increased concentration of the triglyceride plus phospholipid fractions in plasma of fasting subjects, occurs frequently in diabetics,[12] especially those in poor control. In one series, studied before the availability of insulin,[13] blood fat was found to be increased almost as consistently as blood glucose and to provide a better prognostic index. The metabolic fault leading to hyperlipemia apparently involves an excessive mobilization of fat from depots, since hyperlipemia occurs even with low intake of dietary fat.[14] More recently, elevated concentrations of lipoproteins have been demonstrated in groups of unselected diabetics,[15] "poorly controlled" diabetics,[16] patients with nephropathy,[16, 17] and retinitis.[16] Blood cholesterol, on the other hand, shows no consistent changes in diabetes.[18–20]

A marked hyperlipemia often occurs in ketosis, principally due to an increase of triglyceride, with lesser and variable increases of phospholipid and cholesterol concentrations.[21–24] Treatment with insulin over a period of several days restores the concentrations to normal.[22] Serum lipoproteins show variable degrees of elevation,[25, 26] but no consistent response to insulin.

The NEFA fraction, included in some of the older measurements, remained undefined until a more specific method became available.[27] Using this method, Laurell[28] found an elevation of NEFA in three cases of diabetic acidosis. The present work confirms his finding, and shows that an abnormality of NEFA metabolism is detectable even in the controlled diabetic.

ANALYTICAL METHOD

A simple method of extraction and titration, previously described, appears to be suitable for routine clinical work. It has been used in our laboratory for about two years. *Reagents.* Extraction mixture: isopropyl alcohol, forty parts; heptane, ten parts; 1 N H_2SO_4, one part (all solvents redistilled). Titration mixture: 0.1 per cent thymol blue, one part; freshly redistilled ethanol, nine parts (it should be slightly acid to exclude CO_2. The acidity rises excessively with aging, and should be reduced with weak alkali so that 1 ml. is just neutralized with 5 to 10 λ of 0.018 N NaOH). Alkali: approximately 0.018 N NaOH (CO_2-free), made by 1:1,000 dilution of saturated NaOH

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with freshly distilled H_2O, and stored for no more than two days in a reservoir protected with soda lime. It is standardized with each series of titrations by inclusion of a standard solution of palmitic acid in heptane (approximately 600 μEq./L.). *Apparatus*: Microburette, calibrated in micoliters λ) and provided with a reservoir to contain the CO_2-free alkali. Washed N_2 gas, delivered from a tank through a column of alkaline 90 per cent ethanol and then through a capillary reaching the bottom of the titration tube. (The gas must be washed through the alkaline column since tank N_2 always contains traces of CO_2). A relief valve near the titration stand provides control of the gas flow. Titration tubes: standard conical centrifuge tubes, adjusted in position so that the capillary from the microburette ends just above the liquid surface and is washed by splashing when the gas flow stirs and sweeps out the tube. *Extraction*: Add five volumes extraction mixture to one volume plasma, shake vigorously, let stand ten minutes, and then add three volumes heptane and two volumes water. The system should quickly separate into two phases, the upper being clear and colored yellow with carotenoid pigments. *Titration*: 1 cc. titration mixture and 3 cc. upper phase from extraction form a two phase system which is intimately mixed by N_2 flow. Titrate to a yellowish-green endpoint. (A fluorescent light and white background are helpful.) *Calculation*: Subtract titration value of blank (should be 5 to 10 λ) and compute NEFA in plasma (μEq./L.) by simple proportion with the standard, taken through the entire procedure of extraction, sampling and titration.

EXPERIMENTAL PROCEDURE

Glucose, glucagon, fructose, and insulin were administered to normal and diabetic subjects. Duplicate samples of venous blood were obtained shortly before administration of a test agent and at intervals of twenty to sixty minutes thereafter. Blood glucose was determined by a modification of the Nelson colorimetric procedure,[29] and NEFA as described above.

Patients in diabetic acidosis and coma were seen before and during treatment at New York Hospital and at the Hospital of the Rockefeller Institute. In addition to determinations of plasma NEFA and glucose, urinary ketones and sugar were estimated with Clinitest, Ames Co. (copper sulfate, caustic soda, sodium bicarbonate, citric acid), and Acetest, Ames Co. (sodium nitroprusside, aminoacetic acid, disodium phosphate lactose). Plasma CO_2 combining power was measured gasometrically.[30]

RESULTS

The NEFA level of forty fasting, nondiabetic, nonobese subjects averaged 572 ± 280 μEq./L.* In twenty-seven diabetics without ketosis the average was significantly ($p<0.001$) higher, 849 ± 287, and still higher ($p<0.001$) in the ten diabetics with ketonuria, 1,311 ± 466 (figure 1). There was no correlation between elevation of fasting NEFA and glucose. Obese patients, previously reported to have abnormally high fasting NEFA levels, showed a mean fasting value, 862 ± 214, similar to that of the controlled diabetics, although none of the subjects had glycosuria. The relatively great dispersion of NEFA values in all groups shows the lability of this fraction, and emphasizes the need for standard conditions and repeated measurements.

Glucagon (2 mg.) was injected intravenously into nine diabetic and fourteen nondiabetic subjects as a means of producing an endogenous glucose load. The abnormally prolonged elevation of blood glucose, typical of diabetes, was matched with a prolonged but comparatively weak fall of NEFA (figure 2) which differed significantly from the normal response ($p<0.001$ at 40 and 60 minutes).

Glucose (50 gm.), given orally to three diabetic and seventeen nondiabetic subjects, revealed similar abnormalities in NEFA response of the diabetics (figure 3). Fructose (50 gm.), given intravenously to two nondiabetic subjects, caused a decrease in NEFA comparable to the normal response to glucose. A normal response to oral glucose was also seen in one hypophysectomized and one adrenalectomized patient.

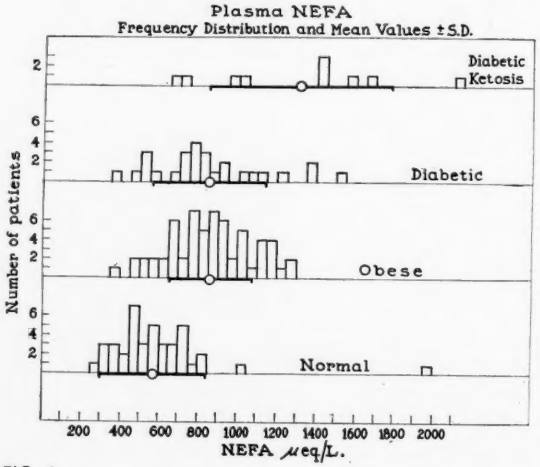

FIG. 1

*All the data given in the paper are represented as the mean ± the standard deviation for each series of observations.

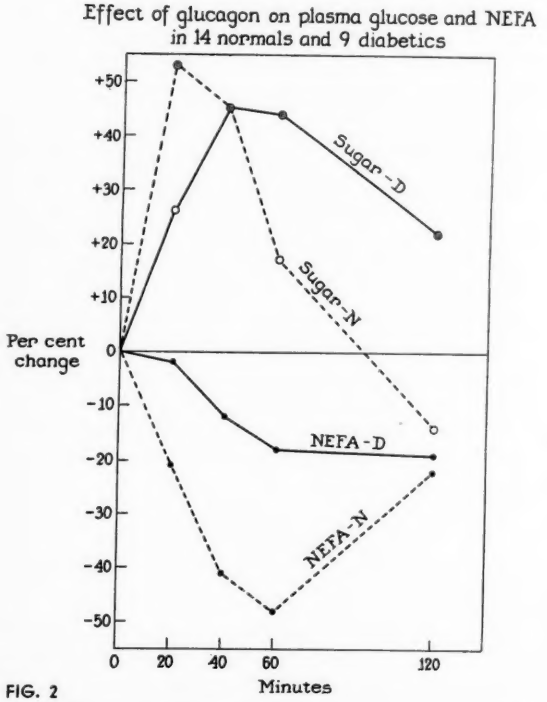

FIG. 2

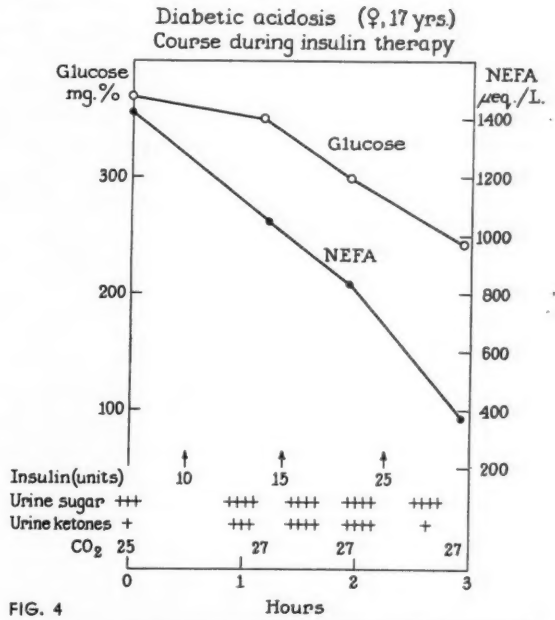

FIG. 4

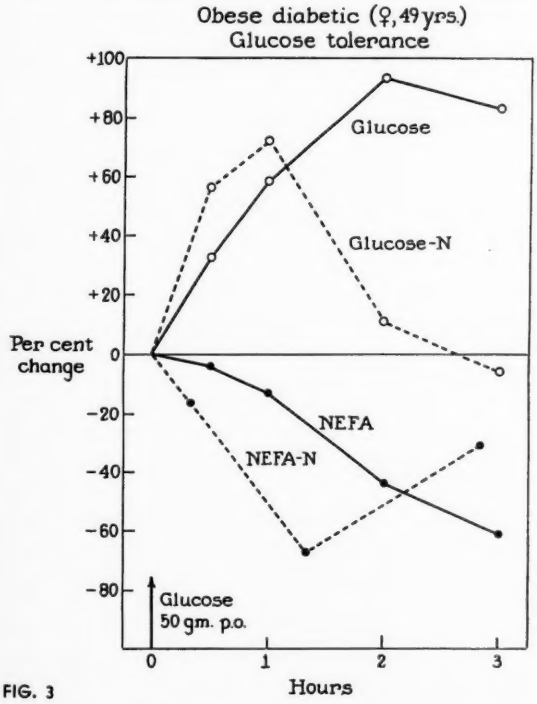

FIG. 3

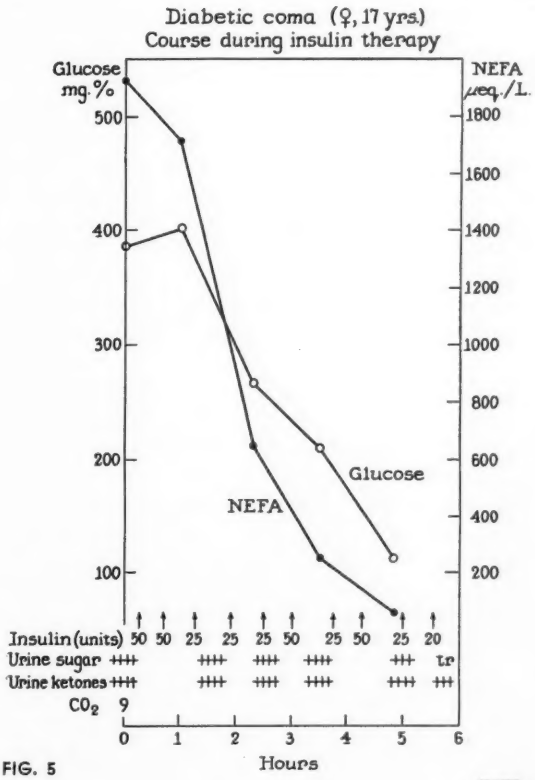

FIG. 5

In diabetic acidosis, eight of the ten patients studied had markedly elevated concentrations of NEFA in nonfasting samples, obtained when the presence of ketosis was determined. Of these, two patients seen at the onset of ketosis, showed a marked elevation of NEFA preceding the rise of urinary ketones (figure 4). Injection of insulin into patients with either mild or severe ketosis (figure 5) caused in each case a prompt reduction of NEFA, correlated with the fall of blood glucose, and preceding by several hours the elimination of ketone bodies.

DISCUSSION

Recent observations suggest that insulin causes a fall in the concentration of NEFA in plasma by inhibiting the release of fatty acids from tissue stores.[2, 3, 31] It appears to have no effect on the removal of NEFA from plasma, since in dogs the clearance of labelled palmitate, bound to homologous albumin, was unaffected by injection of enough insulin to halve the NEFA concentration.[2] These results are in harmony with the observations that insulin promotes the deposition of fat in adipose tissue, [32, 33] while epinephrine, which is ketogenic,[34] and causes a marked increase in NEFA concentration,[5, 6] leads to a depletion of these stores.[33, 35]

It seems probable that the abnormality of NEFA metabolism in diabetes is an impaired ability to limit the output of fatty acids from tissue stores, resulting from an impaired utilization of glucose by the adipose cells. In ketosis, the defect has become extreme, and the body is flooded with a surplus of fatty acids exceeding its capacity for oxidation or synthesis of esters. Treatment with insulin checks the output of fatty acids and removes the primary cause of acidosis, but does not immediately cure ketosis, since the accumulation of ketone bodies in blood and tissues is more slowly removed.

It must be emphasized that this interpretation of ketosis is no more than a working hypothesis, and that the chronic disturbances of lipid metabolism which occur in diabetics have not been studied in relation to NEFA. However, the NEFA system does seem to be important in transport of fatty acids, and it is abnormal in diabetes. Since measurement of NEFA is a relatively simple matter, it might prove useful in the clinic, supplementing blood glucose as an index of diabetic control.

SUMMARY

Diabetic subjects tended to have elevated levels of plasma nonesterified fatty acids (NEFA). Patients in good regulation, seen fasting, averaged significantly above normal, while patients in ketosis showed marked increases. Obese nondiabetic patients resembled the controlled diabetics in elevation of NEFA. The wide range of the data emphasizes the lability of this fatty acid fraction.

Glucose tolerance tests or injection of glucagon in diabetics resulted in an abnormal response of NEFA. The usual sharp fall in NEFA concentration and return to control value was delayed and diminished in amplitude, corresponding to the delayed return of blood sugar concentration.

Injection of insulin into acidotic patients caused a dramatic drop of NEFA concentration, paralleling the fall of blood sugar and preceding by several hours the elimination of ketone bodies.

It is suggested that measurement of NEFA may lead to a more complete clinical evaluation of the metabolic defects in diabetes.

SUMMARIO IN INTERLINGUA

Un Anormalitate del Metabolismo de Non-Esterificate Acido Grasse in Diabete Mellite

Diabeticos tende a monstrar nivellos elevate de nonesterificate acidos grasse (NEAG) in le plasma. Patientes con regulation de grado satisfactori qui esseva examinate in stato jejun habeva valores medie de NEAG significativemente supra le norma, e in patientes in stato de cetosis iste valores esseva marcatemente augmentate. Nondiabeticos obese resimilava in iste respecto le diabeticos in qui le morbo esseva ben regulate. Le extense variabilitate del valores indica le labilitate de iste fraction de acido grasse.

Tests del tolerantia de glucosa o injectiones de glucagon in diabeticos resultava in un responsa anormal de NEAG. Le usualmente acute cadita del concentration de NEAG e le rapide retorno al valores de controlo esseva retardate e reducite in su amplitude, in correspondentia con le retardate retorno del concentration de sucro de sanguine.

Le injection de insulina in patientes acidotic causava un reduction dramatic del concentration de NEAG. Isto esseva parallel al reduction de sucro de sanguine e precedeva per plure horas le elimination de corpores acetonic.

Es suggerite que mesurationes de NEAG resultara possibilemente in un plus complete evalutation del defectos metabolic in patientes con diabete.

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24-Hour Urinary Pepsinogen Excretion in Juvenile Diabetes

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Experimental and clinical evidence points to the fact that the pepsinogen (uropepsin) content in twenty-four hour specimens of urine may measure indirectly the pituitary-adrenal cortical activity.[1-4] It has been well established that disturbances in the pituitary-adrenal cortical physiology play an important role in the so-called diabetic state.[5] We have undertaken therefore to investigate the uropepsin levels in juvenile diabetics.

PROCEDURE

Twenty-four hour urine collections from seventy-four patients with juvenile diabetes mellitus were obtained, and chemical determinations of the total pepsinogen (uropepsin) content of the urines were made according to the method described by Spiro et al.[2] and Gray et al.[3]* The results are expressed as units of undiluted urine excreted in twenty-four hours. Although urine may stand for three days at room temperature without any significant change in uropepsin content,[4] nevertheless, in order to avoid this small loss each large gallon bottle in which the urine was collected contained 5 cc. of 25 per cent sulfuric acid. The diabetic patients ranged in age from nine to thirty-three years, with all but ten patients sixteen years or younger (table 2). These patients were on maintenance diets with insulin coverage when these studies were made. All were engaged in usual activities during the summer season.

RESULTS AND COMMENTS

The results are presented in tables 1, 2 and 3. In table 1, the twenty-four hour uropepsin values of normal subjects, and in table 2, those of diabetic patients are presented in the order of magnitude of the excretion of

TABLE 1

Urine pepsinogen (uropepsin) excreted in twenty-four hours urine of normal children and adults

Patient	Age	Sex	24 Hour Uropepsin Excretion*
1	12½ yrs.	M	900
2	12 yrs.	M	990
3	28 yrs.	M	1,040
4	1½ yrs.	M	1,080
5	26 yrs.	M	1,320
6	3 mos.	M	1,388
7	6 yrs.	M	1,416
8	22 yrs.	M	1,470
9	11 yrs.	M	1,570
10	11 yrs.	M	1,730
11	58 yrs.	M	1,750
12	8 yrs.	M	1,796
13	19½ yrs.	M	1,930
14	16 yrs.	M	1,970
15	15 yrs.	F	2,000
16	13 yrs.	M	2,140
17	26 yrs.	M	2,200
18	29 yrs.	M	2,260
19	9 yrs.	F	2,268
20	13 yrs.	M	2,340
21	12 yrs.	M	2,360
22	26 yrs.	M	2,390
23	9½ yrs.	M	2,400
24	20 yrs.	M	2,540
25	12 yrs.	M	2,560
26	12 yrs.	M	2,880
Mean			1,872.62

*Units.

*pH of urine was carefully adjusted to 1.5 and the hemoglobin substrate as well. They were then incubated at 37°C. for thirty minutes, and the reaction stopped with trichloroacetic acid. A calibration curve was made, using tyrosine and pepsin. The purity of the tyrosine was checked by Kjeldahl determination of the nitrogen melting point and by absorption spectrum. Duplicates agreed within 4 per cent or were discarded. Discards did not amount to more than 1 per cent of the total.

In the case of uropepsin, five urine specimens were analysed immediately after the specimen was obtained, and the same specimens refrigerated and analyzed one week later. The percentage difference was no greater than 8.2 per cent with the average difference being 5.9 per cent. Within any given twenty-four hour specimen, the duplicates are good but the twenty-four hour specimen may vary from week to week, depending on the condition of the patient. Because of significant variations of uropepsin excretion during the twenty-four hour period, studies of single urine specimens or even twelve-hour collections were unsatisfactory. The need for accurate twenty-four hour collections was apparent to us, expressed as units excreted per twenty-four hours. The unit of activity of uropepsin is defined in this study as the amount releasing 0.04 mg. of tyrosine-like substances during a thirty-minute incubation at 37°C. in the standard assay.

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TABLE 2

Twenty-four hour pepsinogen (uropepsin) excretion in urine in juvenile diabetics of varying age and sex and with varying insulin dosage and duration of illness

Case Number	Age in Years	Sex	Insulin Dosage Units	Duration Years	24-Hour Uropepsin Excretion*
1	15	M	46	4	643
2	22	M	60	10	975
3	13	M	70	5	1,020
4	15	F	120	4	1,030
5	15	F	30	4	1,040
6	14	M	75	4	1,060
7	10	M	35	6	1,060
8	12½	F	20	5	1,120
9	9 mos.	M	6	1 mo.	1,152
10	12 yrs.	F	60	8 yrs.	1,160
11	15	M	20	1	1,210
12	10	F	12	3	1,220
13	10½	F	40	6½	1,220
14	14	F	90	7	1,320
15	13	M	50	1	1,460
16	15	M	30	3	1,470
17	14	F	108	8	1,470
18	11	F	50	2	1,500
19	15	F	80	13	1,550
20	10½	F	60	6	1,580
21	13	M	40	5	1,584
22	14	F	70	5	1,600
23	10	M	61	3½	1,610
24	2½	M	24	1	1,720
25	14	F	65	4	1,890
26	12½	F	55	3	1,920
27	9	M	45	2	2,030
28	14	F	40	3	2,040
29	14	M	24	2	2,100
30	13	F	20	1	2,124
31	10	F	25	1	2,169
32	13	M	50	4	2,170
33	13	F	26	6	2,260
34	15	F	80	5	2,360
35	12	M	36	4	2,360
36	8	F	30	3	2,388
37	13	M	43	1	2,400
38	14	F	35	2	2,500
39	12	F	50	4	2,500
40	32	M	54	30	2,500
41	9½	F	30	2	2,664
42	12½	M	47	5	2,670
43	15½	F	55	4	2,710
44	15	M	50	2	2,720
45	26	F	60	17	2,880
46	10	M	32	5	2,900
47	13	F	95	2	3,200
48	11	F	42	3	3,220
49	15	M	100	2	3,230
50	14½	M	75	6	3,320
51	12	F	42	1	3,368
52	15	F	44	10½	3,400
53	27	F	50	18	3,504
54	33	M	60	31	3,676
55	23	M	60	18	3,920
56	15	F	43	5	3,950
57	10	F	45	5	3,960
58	15	M	80	11	4,080
59	10	M	50	6	4,130
60	13	F	45	10	4,240
61	14	M	50	5	4,300
62	16½	M	60	15	4,380
63	15	M	60	10	4,850
64	14	M	77	10	4,880
65	14	M	45	1	5,670
66	22½	F	55	16	5,820
67	13	F	45	8	5,830
68	23	F	55	17	5,832
69	23	M	64	19	6,125
70	14	F	60	9	7,600
71	24	M	65	11	7,650
72	13½	M	58	7	7,800
73	14	M	78	3	7,980
74	14	M	80	8	9,080
Mean					3,000
Standard deviation					±1,920
P					10^{-3} to 10^{-4}

*In units.

pepsinogen, expressed in units. In table 3, the twenty-four hour uropepsin excretion is arranged in columns, according to duration of the diabetic state. Also, individual columns for each year of the first five-year period are included in order to show the relatively low and similar incidences of abnormal values during each of the first five years in contrast to the periods over five years. A horizontal line across each of the columns divides the normal from the abnormal values.

The normal mean value was 1,872 uropepsin units, with a standard deviation of ±549. The average for the diabetics was 3,000 uropepsin units with a standard deviation of ±920 and a P value (comparing to normal) of 10^{-3} to 10^{-4}. The mean for the patients with duration of disease from one to five years, was 2,368 with a standard deviation of ±928 and a significant P value of 10^{-2}; the mean for those with disease from five to ten years was 3,883 with a standard deviation of ±2,820 and a significant P value of 10^{-3}; and the mean for those with disease over ten years was 4,133, with a standard deviation of ±1,680 and a significant P value of 10^{-3} to 10^{-4}.

We note (table 3) that the mean value increases correspondingly and significantly above the normal mean with progressive increase in duration of the diabetes mellitus, and that there occurs a significant progressive increase in number of patients having abnormal values. During the first five years only 20 per cent of all the diabetics had elevated twenty-four hour uropepsin excretion values above 3,000 units, whereas in those of five

TABLE 3

Twenty-four hour pepsinogen (uropepsin) excretion* in urine of normal and diabetic patients

Number of Patients	Normal Patients Control	Arrangement of Patients with Juvenile Diabetes Mellitus According to Duration of Disease: 1 Year	2 Years	3 Years	4 Years	5 Years	1 to 5 Years	5 to 10 Years	Over 10 Years
1	900	1,152	1,500	1,220	643	1,020	643	1,060	975
2	990	1,210	2,030	1,470	1,030	1,120	1,020	1,160	1,550
3	1,040	1,460	2,100	1,610	1,040	1,584	1,030	1,220	2,500
4	1,080	1,720	2,500	1,920	1,060	1,600	1,040	1,320	2,880
5	1,320	2,124	2,664	2,040	1,890	2,360	1,060	1,470	3,400
6	1,388	2,169	2,720	2,388	2,170	2,670	1,120	1,580	3,504
7	1,416	2,400	3,200	3,220	2,360	2,900	1,152	2,260	3,676
8	1,470	3,368	3,230	7,980	2,500	3,950	1,210	3,320	3,920
9	1,570	5,670			2,710	3,960	1,220	4,130	4,080
10	1,730					4,300	1,460	5,830	4,240
11	1,750						1,470	7,600	4,380
12	1,796						1,500	7,800	4,850
13	1,930						1,584	9,080	4,880
14	1,970						1,600		5,820
15	2,000						1,610		5,832
16	2,140						1,720		6,125
17	2,200						1,890		7,650
18	2,260						1,920		
19	2,268						2,030		
20	2,340						2,040		
21	2,360						2,100		
22	2,390						2,124		
23	2,400						2,169		
24	2,540						2,170		
25	2,560						2,360		
26	2,880						2,360		
27							2,388		
28							2,400		
29							2,500		
30							2,500		
31							2,664		
32							2,670		
33							2,710		
34							2,720		
35							2,900		
36							3,200		
37							3,220		
38							3,230		
39							3,368		
40							3,950		
41							3,960		
42							4,300		
43							5,670		
44							7,980		
Mean	1,872.62	2,361	2,493	2,731	1,700	2,546	2,368.40	3,679	4,133
St. Dev.	±549	±1,420	±599	±1,050	±772	±1,210	±928	±2,940	±1,680
P		$1x10^{-1}$	10^{-2} to 10^{-3}	$5x10^{-1}$	$4x10^{-3}$	$1x10^{-2}$	10^{-2}	10^{-3}	10^{-3} to 10^{-4}

*In units.

to ten years' duration, and in subjects with over ten years of disease the values were 46 per cent and 76 per cent, respectively. These elevations are statistically significant as indicated by the P values. We also note a definite and striking progressive increase in elevated values with the increase of the duration of the diabetic state.

DISCUSSION

It is evident from this study that the uropepsin values are higher in patients with diabetes mellitus than in normal individuals and this is especially noticeable in those with disease of longer standing. If twenty-four hour uropepsin excretion in the urine is related to pituitary and adrenal cortical activity,[1-4] one may presume that adrenal cortical activity is increased in many juvenile diabetics, and that it gradually assumes this hyperfunction in a greater number of patients with the continuance of the diabetic state.

TABLE 4

Twenty-four hour pepsinogen (uropepsin) excretion of patients with diabetes mellitus based on duration of the disease

Duration	Total Number of Patients	24-hour Mean Uropepsin Excretion in Units	Standard Deviation	P*	Number and Percentage of Patients Excreting 3,000 Uropepsin Units or Less: Number of Patients	3,000 Uropepsin Units or Less: Per Cent of Total	Over 3,000 Uropepsin Units: Number of Patients	Over 3,000 Uropepsin Units: Per Cent of Total
1 to 5 years	44	2,368.40	± 928	10^{-2}	35	79.54	9	20.46
5 to 10 years	13	3,679	±2,940	10^{-3}	7	53.84	6	46.16
Over 10 years	17	4,133	±1,680	10^{-3} to 10^{-4}	4	23.53	13	76.47
Total series of diabetics	74	3,000	±1,920	10^{-3} to 10^{-4}	46	62.16	28	37.84
Normal patients (control)	26	1,872.62	± 549		26	100	0	0

*The "P" values are for comparisons with normals.

It cannot be answered at the present time whether the greater number of diabetics of long standing with elevated uropepsin is dependent on the metabolic alterations in diabetes mellitus or the progressive decrease of effectiveness of insulin to inhibit the production or action of the anti-insulin factors as pituitary or adrenal cortical hormone, or whether these are independent variables. Unfortunately, almost all of these patients cannot be considered as well-controlled, as is indicated by their significant hyperglycemia and glycosuria throughout the greater part of the twenty-four hour period. It cannot be answered at present, whether completely controlled patients show a lesser tendency.

Another question that cannot be answered definitely is whether during the twenty-four hour period subclinical states of hyperinsulinism did not exist in such patients, resulting in excessive production of epinephrine and stimulation of the hypothalamus-pituitary-adrenal cortical system with successively excessive production and excretion of pepsinogen. However, many of the patients with abnormal values of uropepsin were not satisfactorily controlled before and during the period of study so that it is unlikely that hyperinsulinism did exist in their cases. That insulin itself may be a stimulant of pepsinogen production seems unlikely, since few abnormal values were found in the largest group of one to five years' duration, receiving comparable insulin units per day as compared with a smaller group with longer duration of illness.

It has been postulated by many[5] that the pituitary and the adrenal cortex play an important role in the metabolic disturbance in diabetes mellitus and probably more so in the juvenile diabetic, and that insulin tends to inhibit their excessive action. Klein et al.[6] noted higher corticoid values in juvenile diabetes. Izzo et al.[7] observed greater response to ACTH or steroid injection. Becker and collaborators[8] offer an array of evidence, involving the adrenal cortex in diabetic retinopathy and in Kimmelstiel-Wilson disease. Maengwyn-Davis and collaborators[9] note a significant increase in 17-hydroxycorticosteroid excretion in diabetics with retinopathy. Several clinical reports[10] of striking amelioration of the diabetic state and of the vascular lesions in different tissues in humans, after natural destruction or operative removal of the pituitary or adrenal glands, tend to give further support to the contention that the latter two endocrine glands exercise an important influence upon the disturbed metabolism in diabetes mellitus. This hypothesis, however, needs further and more extensive experimental and clinical observation.

SUMMARY

1. Twenty-four hour uropepsin values are significantly higher in diabetics than in a comparable group of normal individuals.

2. The incidence of higher excretions of uropepsin increases with the duration of the disease.

SUMMARIO IN INTERLINGUA

Excretion de Pepsinogeno (Uropepsina) in le Urina de Vinti-Quatro Horas in Patientes Pediatric de Diabete Mellite

1. Le valores de uropepsina pro periodos de vinti-quatro horas es significativemente plus alte in diabeticos

que in comparabile gruppos de individuos normal.

2. Le frequentia de valores augmentate del uropepsina excernite cresce con le duration del morbo.

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Oculomotor Paralysis in Diabetes Mellitus

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INTRODUCTION

Eye changes in diabetes mellitus have been noted for 150 years.[1] Dieulafoy in 1905 summarized the literature up to that time.[2] The incidence of ocular palsies is controversial, occurring in 0.1 per cent of Waite and Beetham's series of 2,002 diabetics, as compared with 4 per cent of a random series of 457 nondiabetics.[7] (See table 1).

Homolateral temporal or orbital pain occurs frequently,[9] and must be differentiated from aneurysm of the internal carotid artery. Evidences of vascular disease in such patients are hypertension, albuminuria, retinal vessel changes,[4] and hemiplegia. Changes may be present in vasa vasorum, resulting in "neuritis" or "neuronitis," hemorrhage or thrombosis in the intramedullary portion of the brain stem, or mechanical pressure by arteriosclerotic vessels. (See table 2).

Hilgartner,[13] White,[14] and Coutinhon[15] have reported cases with paralysis of the superior rectus and the inferior oblique of the same eye. Coutinhon's case[15] presented hypertensive and arteriosclerotic retinopathy. Camisasca and Salvadori[16] report ocular palsies in conjunction with vascular disturbances of the cochleovestibular apparatus. According to Weinstein and Dolger,[9] occlusion of the posterior inferior cerebellar artery, and pupillary abnormalities are common. Hoffman observed two cases of optic atrophy with glycogen deposits in the optic nerves.[3]

CASE REPORT

On July 29, 1954, a sixty-seven-year-old white male was admitted to The Johns Hopkins Hospital (No. 680320), complaining principally of a drooping left eyelid for the last sixteen days. Diabetes had been diagnosed seven years prior to admission. The patient did have previous episodes of near syncope, urinary frequency, polydipsia, and weight loss. He took insulin, dosage unknown, until four years prior to admission. Efforts at regulation were sporadic. On July 10, 1954, he noted blurring of vision, and diplopia on looking straight ahead. On July 13, 1954, he noted drooping of the left eyelid, followed by aching pain in the left frontal region. Tear formation in the left eye was excessive. X rays of the skull and prostigmine test were negative.

The work reported here was performed at The Johns Hopkins Hospital, Baltimore, Maryland.

PHYSICAL EXAMINATION

T. 98.6, P 80, full and reg. R 18, B.P. 140/80, wt. 137. The patient was a well-developed, well-nourished white male, with almost complete ptosis of the left upper lid which could not be elevated voluntarily. The left pupil was slightly larger than the right, reacting somewhat sluggishly to light and accommodation. Extra-ocular movements were normal in the right eye, but the left eye deviated laterally, with no movement medially beyond the midpoint in the central or diagonal directions. The patient could not move his left eye upward and outward (superior rectus) and could not rotate the eye downward in left lateral gaze (inferior rectus). The mediae were clear, the

TABLE 1

Author	Number of diabetic patients	Number with ocular palsies	Nerve involvement
Hoffman (3)	4,001	16	III (predominantly)
Gray (5)	?	?	III (predominantly)
Leopold (6)	100	5	?
Collier (4)	30	30	Preceded glycosuria
Kaplan (8)	4	4	VI = 3, III = 1
Weinstein & Dolger (9)	14	14	III = 7, VI = 6, III+ VI = 1

TABLE 2

Author	Site of Lesion	Functional Disturbance
Bender and Weinstein (10)	III nerve roots and trunk	Paralysis of levator palpebrae superioris and inferior rectus
	III dorso-rostral nucleus	Paralysis of sphincter-pupillae and inferior rectus
	III ventro-caudal nucleus	Paralysis of levator, superior rectus, medial rectus, and inferior oblique
Eareckson and Miller (12)	III main nucleus	Paralysis III, pupil spared
Weinstein and Bender (11)	midbrain tegmentum	No lid-closure synkinesis in "normal" eye
Kaplan (8)	infranuclear lesion VI	Impairment of lateral gaze without conjugate paralysis

right disc somewhat pale. Punctate reddish areas were present about the left macula with slightly increased arteriole tortuosity and light-streaking bilaterally. A soft, blowing, systolic apical cardiac murmur was transmitted to the axilla. The cranial nerves were normal except for a slight paralysis of the seventh lower motor nerve and complete *peripheral* third nerve palsy with minimal sympathetic involvement (see figure 1). On admission blood sugar was 136 mg. per cent. Urinalysis showed specific gravity of 1.012, and 4-plus reaction for sugar. EKG showed left ventricular strain and left axis deviation. On forty units NPH insulin per day at the time of discharge, his overnight urine revealed 0-1+ sugar varying to 3+ at bedtime. The patient remained asymptomatic except for inability to see with his left eye (ptosis), and a two-day period of "difficulty with vision" in his right eye (sluggishness of downward and outward movement). The patient was observed for three months, his symptoms and signs abating until no demonstrable paralysis was present.

DISCUSSION

At the onset it was apparent that in this patient the peripheral trunk of the third cranial nerve was involved. This was made clear by his inability to elevate the lid, or to move the eye medially, upward and outward, and downward when deviated laterally. Later inability to direct the right eye downwards and outwards signified involvement of the right third and sixth cranial nerves.

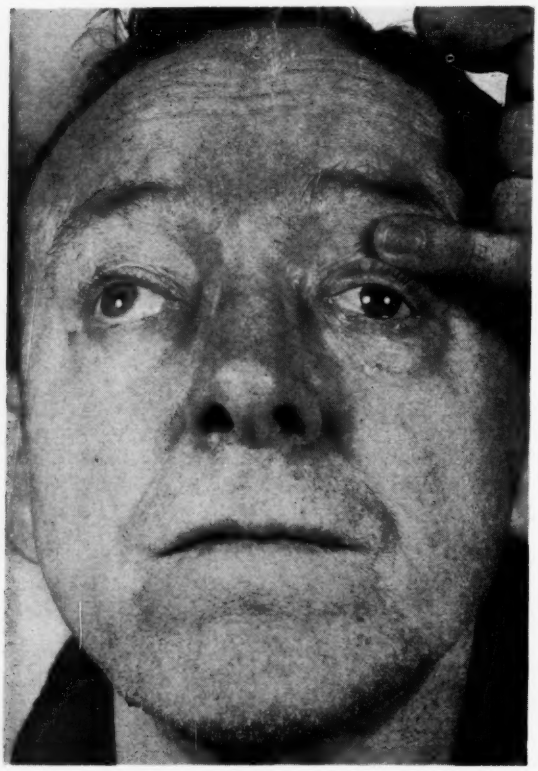

FIG. 1. The patient has been instructed to look to the right and upward. The left upper lid is being supported. (Note excessive tear formation in left eye.)

The history of this patient supports the contention that the neurological lesion accompanying diabetes does not bear any relationship to the duration or severity of the disease, and that probably spontaneous remissions and exacerbations are produced. It appears that "control" of the clinical expressions of diabetes may retard, halt, or reverse the neurological lesion. It is not safe to assume that the disappearance of reducing substances from the urine, or the lowering of fasting blood sugar to below 170 mg. per cent will provide direct control of the pathologic process in tissue. In the presence of disturbed carbohydrate metabolism, neural tissue, depending heavily on glucose and oxygen, may not receive the proper composition of fluids. Also, vascular changes of obscure etiology lead to ischemia of neural tissue. The adjustment of the patient's laboratory findings to a "control" of diabetes, as clinicians understand it, apparently improves the biochemical, if not the histological situation.

SUMMARY

1. A case of diabetes mellitus is reported. The presenting symptoms were visual impairment and inability to raise the left upper lid.

2. The pertinent literature is reviewed and the pathophysiology discussed.

3. Adequate control of the diabetic state by means of proper diet and insulin, if necessary, is stressed as a means of attempting to halt or to reverse ocular paralysis in diabetes mellitus.

SUMMARIO IN INTERLINGUA

Paralyse Oculomotori in un Caso de Diabete Mellite

1. Es reportate un caso de diabete mellite. Le symptomas de presentation esseva defectivitate visual e incapacitate de sublevar le palpebra sinistro-superior.

2. Es presentate un revista del pertinente litteratura e un discussion pathophysiologic.

3. Le regulation adequate del stato diabetic per medio de correcte dietas e, si necessari, de therapia a insulina es indispensabile in le effortio a arrestar o reverter paralyse ocular in diabete mellite.

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Information and the Furtherance of Science

Speaking at the Royal Society conference on Scientific Information in June, 1948, Sir Edward Appleton, who had been awarded the Nobel Prize in physics the year before, said:

> If anyone set himself the task of merely reading — let alone trying to understand — all the journals of fundamental science published, and worked solidly at his task every day for a year, he would discover that at the end of that year he was already more than ten years behind! If the same constant reader (I think we may well call him a constant reader) has included technical literature as well, he would find himself about 100 years behind in his work after twelve months' effort!

Two years ago Professor Bentley Glass of The Johns Hopkins University completed a survey on abstracting in the literature of the biological sciences in which he found that material on this subject, including medicine and agriculture, is drawn from something like 21,000 different serial publications.

This is a matter of grave concern to those who are concerned with the further development of science. Research on ways of recording, retrieving, correlating and using scientific data is today no less important than is research for new data which are often lost in the vastness of already recorded data which glut our swollen libraries.

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The Nature of Diabetic (Kimmelstiel-Wilson) Glomerulosclerosis

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In their original description Kimmelstiel and Wilson[1] remarked on the high degree of arteriosclerosis and fatty degeneration of the arterioles found in most of their eight cases of diabetic intercapillary glomerulosclerosis. They also noted that in many instances continuity could be seen between the hyaline change in the vasa afferentia and the intraglomerular hyaline masses, though they stated that they also observed lesions in glomeruli with afferent arterioles that appeared normal. These findings were corroborated by Allen,[2] who also remarked on the presence of sclerosis of the efferent arterioles in these cases. Bell[3] asserted that the glomerular lesions were never found except with severe involvement of the afferent and efferent arterioles, while Horn and Smetana[4] found arteriosclerosis and arteriolar sclerosis in 94 per cent of eighty-eight cases of the Kimmelstiel-Wilson type of nephropathy. Newburger and Peters[5] advanced the concept that diabetic nephropathy was only one manifestation of a "peculiarly widespread degenerative vascular disease." Bell's[3] demonstration that in diabetes renal arteriosclerosis may occur without hypertension or cardiac hypertrophy adds further weight to this concept.

The part played by lipid in the etiology of the lesions has been disputed. The original workers[1] attached no special significance to it. Koss[6] believes that the lipid appears later during the maturation of the lesions. Wilens and his associates[7] thought that the fat in the lesions might undergo transformation to a hyaline connective tissue, while Hartroft[8] believes that fat emboli and/or lipidic thrombi, together with a possible fundamental disorder in the metabolism and transport of fat, play an important rôle in the genesis of the lesions. Simon[9] speaks of an intercapillary deposit of "lipo-hyalin," and Kent[10] alleges that he found fat embolization in twenty-four of fifty-three diabetic cases.

The contributions of Ballantyne and Loewenstein,[11–12] of Friedenwald,[13, 14] of Ashton,[15–17] and of Becker[18] have established beyond doubt the micro-aneurysmal nature of diabetic retinopathy. Furthermore, the clinical[14, 19] and pathologic[14, 15] correlation of concurrence of diabetic retinopathy and nephropathy is more than suggestive of a common fundamental etiology for these two conditions. We have, therefore, attempted the investigation of renal diabetic lesions from the standpoints of glomerular capillary micro-aneurysm formation, fat changes, hyaline arteriolar sclerosis and hyaline glomerulosclerosis.

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MATERIALS AND METHODS

Routine sections and formalin-fixed material from seven cases of diabetic nephropathy were available; also from one florid case of purely exudative type of nephropathy in a man of thirty-nine years with no clinical or pathological suspicion of diabetes; one case of acute, toxic (alcoholic), thrombotic glomerulonephropathy in a man aged forty-one years (figures 8, 9); six cases of chronic glomerulonephritis, five cases of malignant hypertension, forty-six cases of benign hypertension, together with many cases of other diseases,[20] which served as controls. Paraffin sections were stained with hematoxylin and eosin, Masson's trichrome, Hotchkiss-McManus periodic acid Schiff technic, Gomori's silver oxide[21] and by Gomori's method for hemosiderin;[22] also by dilute carbol fuchsin (1:15 aqueous dilution of Ziehl-Neelsen) followed by 1 per cent anilin blue in 2.5 per cent glacial acetic acid. On frozen sections of formalin-fixed material the following technics were used: (A) modified benzidine-nitroprusside-peroxide, as used by one of us in investigating the nature of hyaline membranes in the lungs.[23] It was found that troublesome crystalline precipitation of the reagents could be minimized by shortening the period of incubation in the benzidine-nitroprusside mixture to three to five minutes. (B) nadi staining:[23] 1 vol. of 1 per cent alcoholic alpha-naphthol and 8 volumes of 1 per cent aqueous dimethylparaphenylenediamine, both freshly prepared, were mixed together; water-washed frozen sections were immersed in this mixture, one volume of three volumes hydrogen peroxide added, and staining allowed to pro-

ceed for three to five minutes, after which the sections were floated out in water and mounted in glycerin-jelly; this technic was used with and without prior lipid extraction in alcohol-ether mixture and in xylene; a theoretical consideration of the substances demonstrated by the nadi technic has been given elsewhere.[24] (C) Dithizone (diphenylthiocarbazone): by this method erythrocytes and free hemoglobin from lysed red blood cells are stained a light yellowish-brown or amber color,[24] probably by virtue of the zinc content of carbonic anhydrase.[25] (D) Hemochromogen development.[24] (E) Fischler's copper method for fatty acids, which also stains the lipoprotein envelopes of red blood cells an intense black color.[25] (F) Oil red O;[21] Light benzidine staining preceding this often gave a more informative picture. In some cases both oil red O-stained and unstained frozen sections were examined by polarized light, both at room temperature and after cooling to 5-10°C. In two cases, showing predominantly nodular Kimmelstiel-Wilson lesions, hematoxylin and eosin stained serial sections were examined.

RESULTS

In all cases of diabetic nephropathy, where polymerizing formalin fixation[25] had not advanced enough to render the reactions negative, the nodular, diffuse and exudative glomerular lesions gave the intense deep blue color of iron-porphyrin compounds[23, 24] with the benzidine and nadi stains (figures 2-6, 14), and an aneurysmal nature of the lesions was suggested in many instances. Focusing at varying depths with the aid of a bright light revealed unmistakable erythrocytes and fragments thereof within some lesions (figures 1, 2, 4, 6 and 14). In the diffuse type of lesion the continuity with the vascular tree of the glomerulus was obvious, and small, mostly peripheral, hemoglobin-positive, somewhat fusiform or conical nodules and ectasias are the rule in this type (figures 4 and 5). In some instances the picture was suggestive of ruptured aneurysms, and many peripheral, hemoglobin-positive lesions were seen pushing into and becoming adherent to Bowman's capsule (figures 2 and 3). The nadi technic stains the lesions intensely and is similar to the benzidine method except that it also stains the lipid globules in the exudative lesions. After lipid extraction the empty lipid spaces fail to stain with nadi reagents, but the diffuse staining of the remainder of the lesion is undiminished by this maneuver. The benzidine staining is never reduced by prior lipid extraction. We always obtained in completely sclerotic glomeruli a diffuse strong staining by both technics.

The lesions, as well as the red blood cells, were stained strongly by Fischler's method (figure 7), and Fischler-positive and benzidine-positive casts were occasionally found in the tubules. Gomori's stain for hemosiderin frequently revealed small amounts of hemosiderin and/or small numbers of hemosiderin-positive erythrocytes within the exudative lesions. Dithizone staining showed the lesions in shades varying from canary yellow to light amber. Hemochromogen development almost invariably revealed the lesions to contain many clusters of tiny cherry-red crystals. The small size of these crystals and the impossibility of counterstaining rendered photography and spectroscopy impossible, but their precise location within the lesions left no doubt as to their significance.

With oil red O staining we have never been able to convince ourselves that the fat is embolic in the diabetic lesions. Rather do we obtain a diffuse staining of moderate intensity, often with the appearance of numerous fine and medium-sized lipid globules. Examination by polarized light demonstrated typical Maltese cross birefringence in some of the lipid vacuoles. This, however, often disappeared at room temperature, but could be made to reappear on cooling.

In the cases of benign hypertension found to show Kimmelstiel-like lesions discrete, hemoglobin-positive nodules were found to be very few in number and irregular in outline.[20] In such cases the picture was that of a more acutely destructive and often hemorrhagic process. In the one case of glomerulonephritis which displayed renal lesions approaching the Kimmelstiel type this was of lobular type[26] and revealed peripheral glomerular, hemoglobin-positive nodules, but these were much smaller and more sclerotic than the diabetic variety.

DISCUSSION

The concept of micro-aneurysmal formation in the Kimmelstiel-Wilson lesions is not new or unexpected. Anderson,[27] using conventional methods and stains, found capillary aneurysms in fourteen of ninety-two cases, but asserted that aneurysms and hyaline nodules are rarely found together, and that aneurysms are not found where the latter are prominent. Anderson described the aneurysm walls as being markedly thickened by a hyaline substance, usually covered by endothelium, and he described the presence of erythrocytes in the laminated hyaline material. Hitherto, the site of the lesions has been the subject of much controversy. Many workers have favored an intercapillary or mesangial site.[1, 28, 30] Allen[2] and Bell,[3] with others,[6] believe the lesions to be

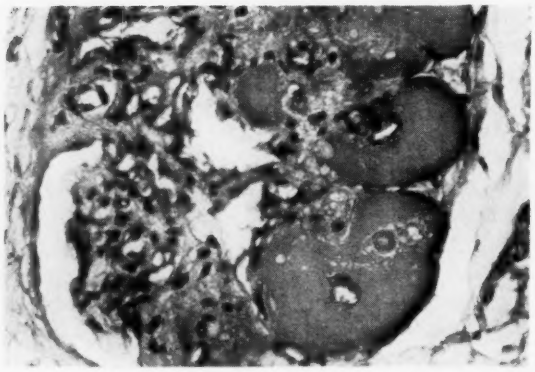

FIG. 1. Exudative lesions: Nondiabetic case showing severe nephropathy with all lesions of this type. Erythrocytes and lipid droplets are seen within the lesions. Dilute carbol fuchsin and anilin blue. X 285.

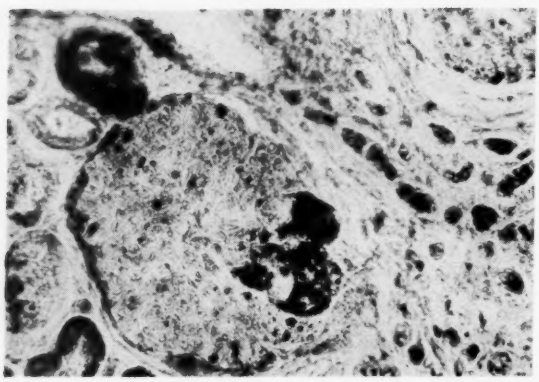

FIG. 2. Case of diabetic glomerulosclerosis showing nodular peripheral lesions containing erythrocytes and benzidine-positive material. This case showed only nodular lesions in routine sections. Benzidine. X 135.

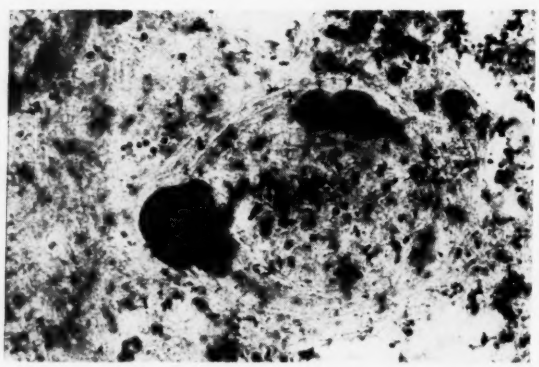

FIG. 3. Three peripheral, exudative lesions are pressing into Bowman's capsule. Frozen section. Benzidine stain. X 135. Note limiting membrane about lesions.

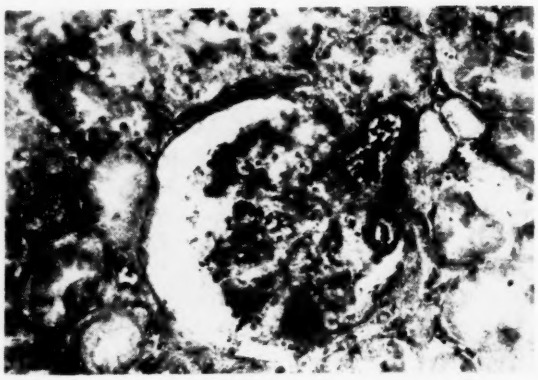

FIG. 4. Diffuse type of diabetic glomerulosclerosis. A small solid lesion is seen at the periphery; also an open one, or small aneurysm to the right near the hilus. The wall of the afferent arteriole is thickened and stains intensely. Benzidine. Frozen section. X 135.

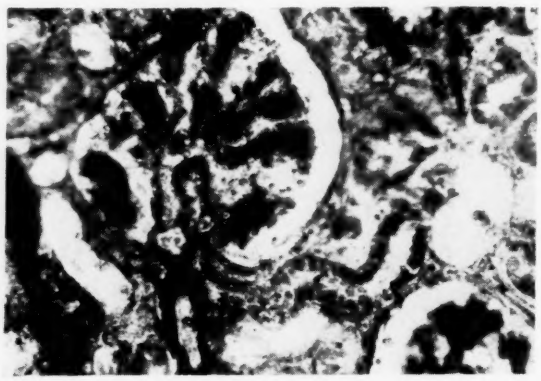

FIG. 5. Diffuse type of diabetic glomerulosclerosis. The continuity of the small, benzidine-positive nodules with the vascular tree is evident. Frozen section. Benzidine stain. X 135.

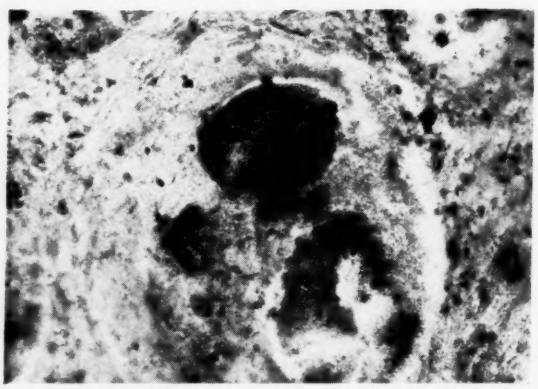

FIG. 6. Nodular diabetic glomerulosclerosis. There is diffuse staining, and the lesion appears to contain fragments of erythrocytes. Routine sections of this case showed almost exclusively nodular lesions. Frozen section. Benzidine stain. X 285.

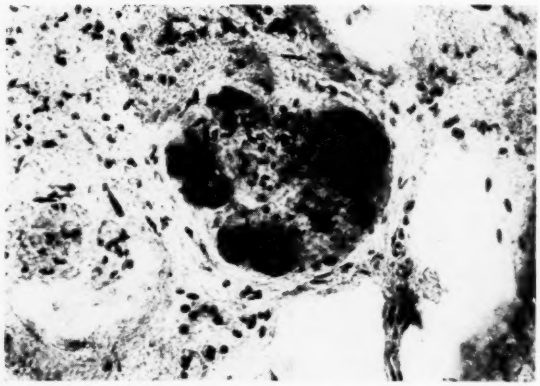

FIG. 7. Peripheral exudative lesions staining intensely by Fischler's method. Frozen section. X 135.

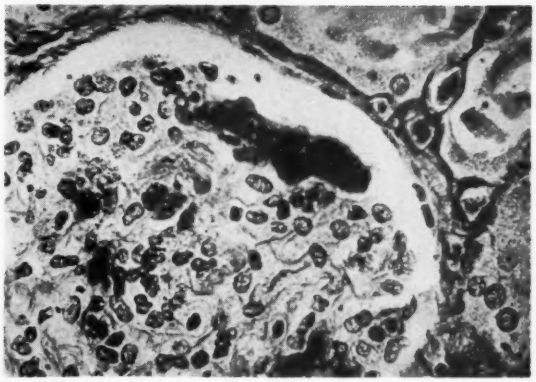

FIG. 10. Same case as figures 8 and 9, stained by Gomori's silver oxide. The capillary near the top of the glomerulus is filled with fused erythrocytes, which stain intensely. X 285.

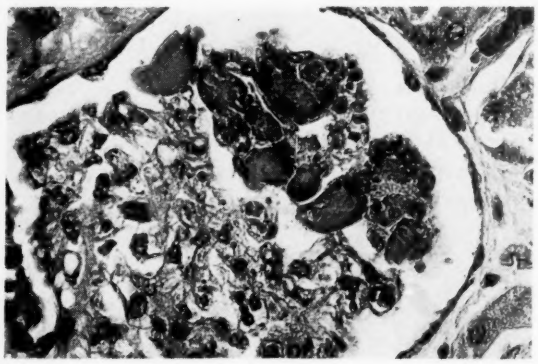

FIG. 8. Glomerulus from case of thrombotic glomerulonephropathy. H. & E. X 285.

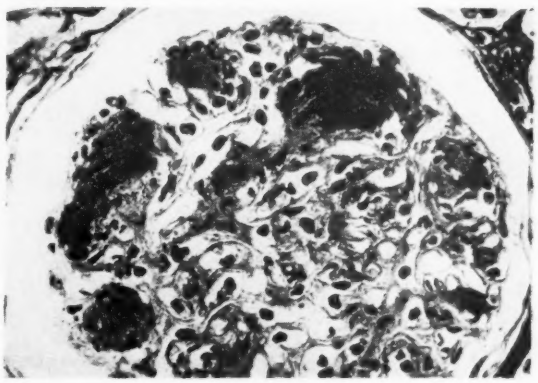

FIG. 11. Nodular Kimmelstiel-Wilson lesions showing lamination by silver oxide staining. X 285.

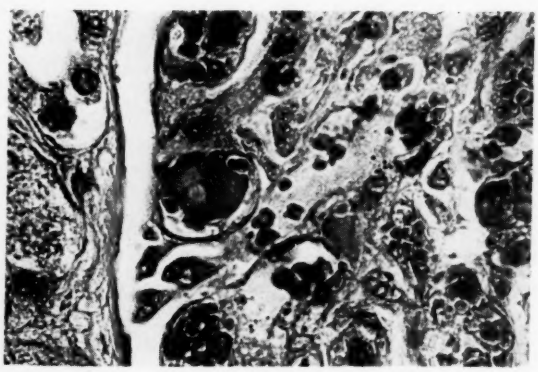

FIG. 9. Same as figure 8 showing fused thrombotic mass occupying lumen of dilated capillary. H. & E. X 480. These fused erythrocytic masses are strongly argyrophilic. See figure 10.

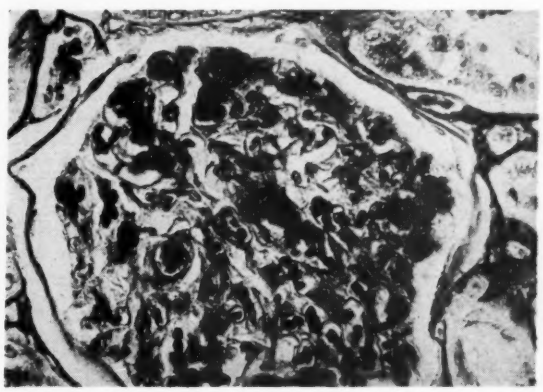

FIG. 12. Glomerulus from diabetic showing a number of small micro-aneurysms, or, at least, dilated capillaries containing fused, argyrophilic erythrocytes. Gomori's silver oxide stain. X 285.

FIG. 13. Exudative lesions showing argyrophilia. X 285. Gomori's silver oxide.

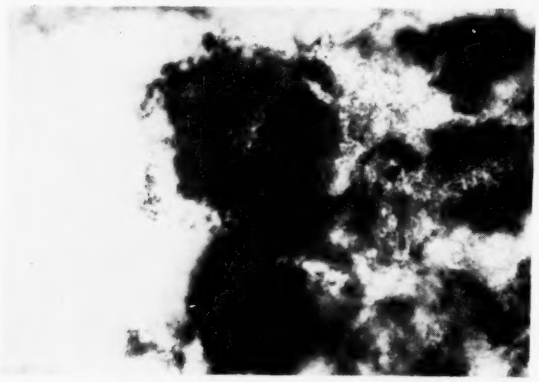

FIG. 14. Two peripheral nodular glomerular lesions. In the top one a small cluster of erythrocytes may be seen in the center of the lesion. Frozen section. Benzidine stain. X 480.

intramural, and that the fundamental pathology consists of splitting and hyaline thickening of the capillary basement membranes. For our part, while we are cognizant of the delimiting structural and probable controlling functions of the capillary basement membrane, we find it impossible in pathologic lesions to say precisely that we are looking at a splitting or reduplication of this vital membrane rather than at a laminated deposit of a material which stains similarly. We have noted that in normal capillaries these membranes are stained rather strongly by both the benzidine and nadi technics, and from this we assume that they contain an iron-porphyrin compound, which, possibly, forms part of an enzyme system, e.g., cytochrome oxidase, that may be concerned with solute transfer across the membranes.

The size of retinal aneurysms (30-90 μ)[12] corresponds to that of the nodular glomerular lesions. As to shape, Ballantyne[12] and Ashton[15] have noted that, whereas the vast majority of retinal aneurysms are round or spherical, some are sausage-shaped. In our experience the same observation applies to glomerular lesions. It is noteworthy that almost all ophthalmic pathologists have stated that capillary stasis and ectasia precede the development of aneurysms,[11, 15] and this has its counterpart in the glomerular capillary dilatation remarked upon by so many general pathologists.[1, 2-28] The same capillary ectasia has been noted to be the first change in the experimental production of glomerular lesions in rabbits by cortisone administration, bearing some resemblance to the human variety.[6, 31] It is common knowledge that the retinal lesions are often surrounded by an exudate, which in some cases may be frankly hemorrhagic.[11-13, 17, 18] Likewise, one may expect that the weakened, anoxic wall of an ectatic capillary or actual aneurysm in a glomerulus allows some of the luminal contents to seep through and occasionally to rupture into the mesangium. Hartroft[8] envisaged such seepage as of possible prime importance in the genesis of the human lesions. If this were the case, the process and deposits, while primarily and chiefly endocapillary in position, could be secondarily and partially extracapillary or mesangial in location, and also apparently intramural. The less common diffuse type of lesion[3, 28, 32] appears to us to develop through a process of axial sclerosis, possibly due to endomural encrustation of mildly but diffusely ectatic capillaries before peripheral nodules (aneurysms?) of any size make their appearance. Of course, both nodular and diffuse types of lesion may co-exist in the same glomerulus.[28] Many workers have emphasized that the early nodular lesions appear to be surrounded by engorged and dilated capillaries.[1, 9, 28] Studies which we have made by serial section technic on normal kidneys appear to explain this on an anatomic basis. We have noted that the afferent limb of the glomerular capillary loop almost invariably takes a peripheral course, at least terminally, and that its peripheral "end" frequently forms a half spiral around the "beginning" of the efferent capillary, which occupies a more central or more juxta-axial course in the glomerulus. In this connection it is noteworthy that the vast majority of retinal micro-aneurysms occur on the venous side of the capillary.[12, 17] The efferent capillary limb, as the site of possible aneurysm formation, is further favored by the consideration that the blood in its passage through the tuft loses some 20 per cent of its fluid content,[8] so that the efferent limb will contain a more viscid as well as a more anoxic blood. Nevertheless, although it appears possible that most of the nodular lesions develop by a process of occlusive

endomural encrustation of micro-aneurysms on the efferent side of the tuft capillary, it is possible that some lesions are formed by adhesion and fusion of adjacent varicose loops.[2, 17]

Since we have found all three types of glomerular lesion, viz. nodular, diffuse and exudative, similarly and equally reactive to both benzidine and nadi technics we have attempted to avoid any strict distinctions among these lesions. However, present concepts demand some discussion. At the outset, while we accept the morphologic identities and individualities of the lesions, we do not feel compelled to seek a fundamentally different etiology in each case. We see no reason to disagree with Bell's[33] morphological distinction of the classical nodular lesion from the diffuse form described by Spühler and Zollinger.[34] The emergence of the "exudative" lesion as an entity, as LeCompte[35] points out in a remarkably clear and balanced review, has been gradual and almost unobtrusive, though it has gained momentum in recent years. However, though it has undeniably been established as morphologically distinct by the descriptions of such workers as Spühler and Zollinger,[34] Koss[36] and Barrie and his associates,[37] we can not help wondering whether this specificity is merited in anything beyond morphologic grounds. Anderson[27] believed that its difference from the nodular lesion was one of degree rather than kind. Koss[36] was unable to locate the material precisely in the layers of glomerular structure. Barrie, Aszkanazy and Smith[37] stated that the material "first appears in the convexity of the capillary loop between the endothelial cell and the glassy membrane." However, figure 2 of these authors could be interpreted to show a completely occluded capillary equally well, as it conveys the authors' idea of a fibrin cap "outside endothelial cells of glomerular tuft." The fact that controversy about the site of the deposits smoulders after so many years is surely indicative of the handicap of traditional histological methods in deciding the anatomical nomenclature of a particular glomerular cell. However, we do not wish to take issue on differentiation (or lack of it) by site alone. Spühler and Zollinger[34] described these lesions as staining red with trichrome, and we agree that most do stain red with Masson's trichrome. Nevertheless, in many instances we have noted that with this stain part of the same lesion may stain red and part green, i.e., there is evidence of physico-chemical maturation towards adult connective tissue. Barrie and his associates[37] used Laidlaw's silver technic and found these lesions to be non-argyrophilic. Using Gomori's silver oxide method we have found that such lesions are argyrophilic, and that they even show early lamination (figure 13). Again, in all instances where we have found Kimmelstiel-like lesions in diseases other than diabetes[20] these lesions have all been of exudative type. Furthermore, it is recognized that experimental cortisone-induced lesions in rabbits resemble more the exudative type,[35, 38] and these experiments have all been of relatively short duration. For these reasons we consider the "exudative" lesion as possibly the earliest of all diabetic renal lesions. To our knowledge there are no studies which show that this lesion cannot mature into connective tissue, and that such maturation may not produce a lesion indistinguishable from the nodular form. Indeed, Barrie and his coworkers[37] convincingly suggest that situation and accessibility of the lesion to organizing cells are all important in this connection, but this must surely not be interpreted as meaning that the glomerular exudative lesion will not slowly mature over long periods. It is probably trite to make remark here of the unreliability of differentiation based on stains alleged to be specific for fibrin. More definite decisions may be forthcoming through employment of technics such as those based on fluorescein-labeled anti-fibrin antibodies.[39] LeCompte's[35] summation of the exudative lesion as appearing rather late has more than a little merit. Indeed, it is conceivable that this lesion may be truly exudative or insudative and derive from rather massive seepage through grossly diseased capillary walls, or from rather abrupt ballooning of such walls.

In regard to lipids in the genesis of the lesions, it is pertinent to state that it is generally agreed that in carefully controlled diabetics there is no lipemia,[9] and that insulin therapy has certainly not reduced the incidence of the nephropathy.[4, 19] However, from an ectatic capillary there may be a greater than usual loss of nonlipid fluid through its wall, which may be impaired as filter by the process giving rise to the dilatation, so that by concentration due to loss of fluid, a not inconsiderable increase in lipid within the lumen may take place. This may be increased by unmasking of lipid from the lipoprotein envelopes of red blood cells,[40] should these be entrapped. In diabetic retinopathy Ballantyne and Loewenstein[11] described the presence in the capillary endothelial cells of abundant fine lipid droplets as one of the earliest changes. We have seen this many times in the glomerular capillaries of diabetics. This local concentration of lipids assumes even greater importance in the light of recent findings in regard to their possible acceleration of, or predisposition to, local clotting of blood constituents,[41] which in turn appears to be due to the high concentration of ethanolamine phosphatide in the chylomicra.[42]

Though the genesis of atheroma and of diabetic glomerulosclerosis and retinopathy may share certain features, there are, nevertheless, obvious dissimilarities: e.g., Friedenwald[14] and Ashton[17] were unable to find micro-aneurysms in the retinae of elderly arteriosclerotics. This would seem to imply a fundamental difference in the case of diabetics prone to develop nephropathy. Such a difference in the "milieu interieur" of these diabetics has been suggested by Zubrod and his associates.[43] Again, Becker[18] has described structural and postulated functional abnormalities in the adrenals of cases of Kimmelstiel-Wilson nephropathy. Rich and his associates,[31] Becker,[18] Stumpf and Wilens,[6] and Bloodworth and Hamwi[38] have produced in rabbits certain glomerular lesions by the administration of cortisone which most nearly resemble the exudative type of human lesion.[35, 38] Becker[18] claims to have produced typical nephropathy and early retinopathy in alloxan-diabetic rabbits given ACTH, and says that he has noted the development of diabetic-type retinopathy in two patients under treatment with ACTH, and that the retinopathy disappeared on withdrawal of the hormone. Jacobs[44] has shown that the plasma seromucoid, bound glucosamine, parallels remarkably the level of the blood sugar in diabetics, and LeCompte reviews the findings of other workers in the field of abnormal mucopolysaccharide patterns in the blood of diabetics.[35] Layton's[45] work suggests that cortisone may inhibit sulfate fixation by tissues, and thus may lead to decreased formation of tissue mucoids by inhibiting the system which synthesizes chondroitin sulfate. Such a mechanism could explain the capillary ectasia produced by cortisone on the basis of weakening of ground substance in the capillary wall.

With regard to the arteriolar changes, the studies of Montgomery and Muirhead[46–48] have demonstrated that the hyaline substance in hypertensive arteriolar walls contains compounds which are identifiable in normal smooth muscle, and they conclude from this that the hyaline material derives from a physico-chemical alteration of the smooth muscle of the arteriolar walls. The same workers have, however, observed an apparent increase in concentration of some of the components, e.g., lipids, carbohydrates and potassium in hyalinized arterioles as compared to normal ones, and they believe that the subendothelial location of the hyaline substance in some instances results from the flow of hyaline material of medial origin through the fragmented internal elastic membrane. They have further found that the lesions of malignant arteriolar sclerosis differ from those of the benign variety in containing acid phosphatase. A number of recently reported cases of acute arterial and arteriolar necrosis following resection of aortic coarctation[49–51] appear to establish the physical nature of such necrosis and to lend support to the observations of Montgomery and Muirhead. However, it may be that the latter authors' interpretation of the source of the hyaline material may well have to be broadened. It is possible that the hyaline subendothelial thickening of hypertensive arterioles may be contributed to by gradual deposition of homogenized blood constituents. Secondly, in severe forms of hyperpiesia, the pile-driving force of the systole may force blood constituents into the vascular walls. In benzidine and nadi-stained frozen sections from both benign and malignant hypertensive cases we have been impressed by the numbers of fragmented erythrocytes in the lumina, and sometimes also in the walls of the arterioles. Homogenization and degeneration of such mural insudates may lead to hyaline thickening in addition to that caused by the transformed media, and could account for the increase in lipids, potassium and carbohydrates, observed by Montgomery and Muirhead, while the presence of acid phosphatase in the arteriolar walls of malignant hypertensive cases very probably derives from red blood cells. We have remarked on the presence of hemoglobin in the subendothelial layers of blood vessels as determined by microspectroscopic means.[24] By plotting at 2 millimicron intervals the absorption curves of lysed erythrocytes suspended in (a) lipemic plasma; (b) nonlipemic plasma; (c) distilled water, we have concluded that the very high absorption by hypertensive arteriolar walls in the wave length range 250-290 mμ noted by Montgomery and Muirhead[48] is due merely to protein. From all these considerations it appears that there is no single substance "hyalin," but that hyaline material is a mixture of proteins, carbohydrates, lipids and iron-porphyrins, and may be derived from physico-chemical transformation of smooth muscle (medial hyaline arteriolar sclerosis), or from homogenization and concentration of blood constituents, including erythrocytes (hyaline membranes in lungs and possibly also intimal and subendothelial hyaline arteriolar sclerosis), or from a mixture of these two processes (many areas of hyaline arteriolar sclerosis with varying appearance especially in malignant hypertension). This concept is not at variance with the findings of Sommers, Crozier and Warren,[52] who found a similar ultraviolet absorption pattern in various types of hyaline arteriolar scleroses, including that occurring in diabetes, but a different and rather specific absorption pattern in the case of glomeruli in diabetic subjects.[53] The fact that this pattern was given by both diseased and apparently healthy glomeruli in diabetics would

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appear to exclude the hyaline material as being responsible, and to point to a more fundamental cause, e.g., possible alterations in the glomerular stromal tissues.

The peculiar behavior of the lysed hemoglobin which we have demonstrated in the glomerular lesions deserves comment. Consideration of somewhat similar situations elsewhere, e.g., in endoluminal vascular clots (aneurysms and coronary arteries), and in the corpus luteum, makes it apparent that high local lipid concentrations may possibly be the cause of the delay or prevention of splitting of hemoglobin. Such a protective effect of lipids on hemoglobin has been postulated and discussed at length by Hartroft and Ridout.[54] It appears to us that this protective effect of lipids on hemoglobin is operative in the Kimmelstiel-Wilson lesions, though our search for hemosiderin in these lesions has revealed that there is some splitting of hemoglobin, albeit very little. Hartroft and Ridout[54] have demonstrated granules of hemosiderin in the lumina and walls of the renal tubules of their choline-deficient rats, in which they claimed to have found lesions resembling the Kimmelstiel-Wilson type. Considering these observations we would suggest that benzidine staining of the centrifuged urinary deposit may be helpful in the clinical diagnosis of Kimmelstiel-Wilson nephropathy by revealing hemoglobin-containing granules or casts. The presence of anisotropic lipid in the urine of patients suffering from diabetic glomerulosclerosis[55] may be due to rupture of peripheral glomerular lesions.

In conclusion it appears that all three types of diabetic glomerular lesions are rich in hemoglobin. By analogy with retinal lesions it is very probable that the basis of many of the lesions in the glomeruli is aneurysmal, though we feel that limitations of materials and methods do not allow us to claim a firm micro-aneurysmal etiology for the lesions. It is probably true to say, however, that were the retina not the physically simple structure that it is—capable of being mounted and examined under the microscope, even after injection technics—the micro-aneurysmal nature of diabetic retinopathy would not be now on the firm footing which it enjoys. The fact that most experienced and careful observers of suitably stained paraffin sections have obviously failed to define endothelium or basement membrane consistently in relation to the lesions excuses our failure to define it in frozen sections. Indeed, the existence is most unlikely of endothelium and basement membranes whose structure is demonstrable by any technic, since in most of these lesions they will long have been destroyed or will have merged with the deposited material. In support of the contention that the lesions consist chiefly if not entirely of concentrated blood constituents it may be mentioned that other workers have drawn similar conclusions from findings based on less specific technics.[35] In further support of our concept we have introduced into this study the case of thrombotic glomerulonephropathy. It will be seen from the illustrations (figures 8-10) that the fused mass of erythrocytes within some glomerular capillary loops of this case stain intensely by the silver oxide technic of Gomori. On this account, and in view of the evidence already adduced in this study, it is our belief that the argyrophilia of Kimmelstiel-Wilson lesions is due to their content of lysed red blood cells. Furthermore, serial section studies of two cases of predominantly nodular type Kimmelstiel-Wilson cases have revealed that some typical nodules contain a central small lumen in which erythrocytes are occasionally seen, i.e., they probably represent micro-aneurysms whose walls have become enormously thickened.

SUMMARY

1. Benzidine-nitroprusside and nadi staining technics were applied to frozen sections of the kidneys of seven cases of diabetic nephropathy and one case of apparently nondiabetic etiology.

2. With these technics all three types of lesions, viz. nodular, diffuse and exudative, stained intensely.

3. These findings, coupled with positive hemochromogen tests, dithizone and Fischler staining, establish that the lesions contain hemoglobin in free and diffuse form. In addition many lesions were seen to contain both intact and fragmented erythrocytes.

4. Evidence for the micro-aneurysmal nature of the lesions is discussed, but is regarded as yet incomplete.

5. Evidence is presented to show that the argyrophilia of the Kimmelstiel-Wilson lesions probably depends on their content of lysed erythrocytes.

SUMMARIO IN INTERLINGUA

Le Natura de Diabetic Glomerulosclerosis de Kimmelstiel-Wilson

1. Le technicas de coloration a benzidina-nitroprussido e nadi esseva applicate a sectiones congelate del renes de septe casos de nephropathia diabetic e un caso de nephropathia de etiologia apparentemente nondiabetic.

2. Per medio de iste technicas, omne le tres typos de lesiones, i.e. le typos nodular, diffuse, e exsudative, acceptava un coloration intense.

3. Iste constatationes — insimul con positive tests a hemochromogeno, dithizon, e coloration de Fischler—establi que le lesiones contine hemoglobina in forma libere e diffuse. In plus, esseva constatate que multe lesiones

contineva erythrocytos tanto intacte como etiam fragmentate.

4. Le existente probas pro le natura micro-aneurysmal del lesiones es discutite sed considerate como non ancora complete.

5. Es presentate datos in supporto del these que argyrophilia del lesiones de Kimmelstiel-Wilson depende probabilemente de lor contento de lysate erythrocytos.

ACKNOWLEDGMENT

Our thanks are due to Mr. L. D. Mellor, F.I.M.L.T., S.T., for plotting the spectophotometric absorptions of the plasma-red cell and red cell-water mixtures. The Beckmann model DU was used for this.

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Oral Administration of Amino Acids

The oral administration of amino acids for therapeutic purposes was based originally on a misconception concerning the digestive capacities of the human gastrointestinal tract in emaciation, in disease, and after surgery. Actual feeding experiments have proven, however, that even in extreme starvation proteins can still be digested as long as food can be swallowed. It is only in the final stages of starvation that digestion is inhibited, and the experiences in the western Netherlands indicated that there is no treatment available which would resuscitate such cases.[1] It was also observed that protein digests were soon rejected and vomited by the patients, and still another disadvantage was the relatively large quantity of liquid which had to be consumed along with the amino acids. When glucose was mixed with the protein hydrolysates, they were somewhat better tolerated, but, as a matter of fact, undigested skim milk-glucose mixtures were preferred by the patients who maintained their weight more effectively. The therapeutic use of protein hydrolysate in malnourished South African children provided equally disappointing results.

The use of protein hydrolysates was particularly recommended in cases of gastrointestinal diseases. It has been shown, however, that protein digestion and amino acid absorption in diseases like peptic ulcer, or ulcerative colitis, or regional enteritis are nearly normal and the use of hydrolyzed protein in such conditions seems to be unnecessary.[2] All these experiments prove that the practical value of "oral" amino acid preparations has been seriously over-emphasized. These preparations are most valuable dietary sources of nitrogen for short-term feeding in those cases where protein digestion is grossly disturbed or in cases of certain food allergies; but, because of their relatively higher cost, their low palatability, and their possible noxious effects cited above, they do not seem to be generally a practical source of nitrogen. The practice of giving a fraction of the daily nitrogen requirement in the form of amino acid drinks or tablets may have its psychological value but is obviously of no particular nutritional importance.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D., Philadelphia, Lea & Febiger, 1955, Chapter "Digestion, Absorption and Metabolism of Protein" by Ernest Geiger, M.D., Ph.D., pp. 106-07.

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Electron Microscopy of the Normal Islets of Langerhans

Studies in the Dog, Rabbit, Guinea Pig and Rat

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The purpose of this project was to study the normal ultra structure of the islets of Langerhans in those animals that are utilized commonly in experimental diabetes. Electron microscopic identification and differentiation of alpha and beta cells of the guinea pig, rabbit, dog and rat have been accomplished previously by comparing the same cells observed in a low-power electron micrograph and in a contiguous, stained thick section.[1] Since islet cells could be recognized and differentiated on the basis of their low-power electron microscopic appearance, further studies were made on their normal ultra structure and on the capillaries and nerve fibers in the islets using higher powers of magnification.

MATERIALS AND METHODS

Six guinea pigs, five rabbits, five dogs and six rats, all adult, were used. They were killed either by a blow to the head or by intravenous nembutal. A portion of the tail of the pancreas was removed rapidly and covered with a few drops of osmic-dichromate fixative.[2] The tissue was cut into small (1 mm.) pieces, while so immersed in the fixative, and then fixed at room temperature in 3 to 4 ml. of osmic acid-dichromate fixative buffered to a *p*H of 7.2 or 7.6 for a period of either one or two hours. The method of dehydration and embedding the tissue in methacrylate was the same as previously described.[1]

Sections of the pancreas were cut with glass knives on a Servall microtome. The islets were localized within the blocks of pancreas by examining relatively thick sections (2-3 μ) with a phase microscope. After finding the islet, the block was trimmed to include only the islet and a small rim of acinar tissue. Thin sections of the islets were examined in an RCA electron microscope (EMU 2D and 2E) without removing the plastic. The initial magnifications used ranged from 3,000-7,000 diameters, and the electron micrographs were then enlarged photographically as desired.

Calibration of the electron microscope at different levels of magnification was made by means of a replica of a 1.75 micron grating. Since this procedure was not done routinely throughout the course of the project, the measurements obtained from the electron micrographs are only approximate values. An approximate, average diameter of the granules was obtained by measuring their greatest diameters on the enlarged photographs. These average values were used to illustrate differences or similarities in size which were apparent on visual examination of the electron micrographs.

The islets of Langerhans of the hamster, mouse, monkey and man were also examined with the electron microscope but a positive identification of the alpha and beta cells in these animals has not yet been obtained.

OBSERVATIONS

Beta Cells

Dog: The nuclei of the beta cells are irregular in contour and have a lobulated appearance in some instances (figure 1). A double nuclear membrane is present in the islet cells of the dog and in all of the species of animals examined.

Most striking as an electron microscopic feature of the beta cells are the beta granules (figure 1). The majority of the beta granules have a rectangular profile, and each is found in a clear area bounded by a distinct membrane. Usually, they extend completely across the clear areas. Individual granules occasionally appear club-shaped or assume the form of a V or T. They do not appear to have any distinct internal structure. Their shape was not affected by two different types of fixatives. The granules have a rectangular profile with fixation in osmic acid (*p*H 7.2 to 7.6) and in 10 per cent formalin buffered to a *p*H of 7.6. This rectangular configuration was not observed in any of the other species examined.

The ergastoplasm, which is composed of membranes

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FIG. 1. Electron micrograph of portions of three beta cells of the dog. The nucleus (N) of the lower beta cell appears lobulated. The majority of the beta granules (GR) have a rectangular profile and are surrounded by a clear space. Mitochondria (M) are scattered throughout the cytoplasm. The ergastoplasm (ER) is abundant and is composed of membranes with associated small granules. A portion of a prominent Golgi complex (G) is present in the upper beta cell. The ergastoplasm of an acinar cell (AC) is present in the upper right-hand corner. X18,000.

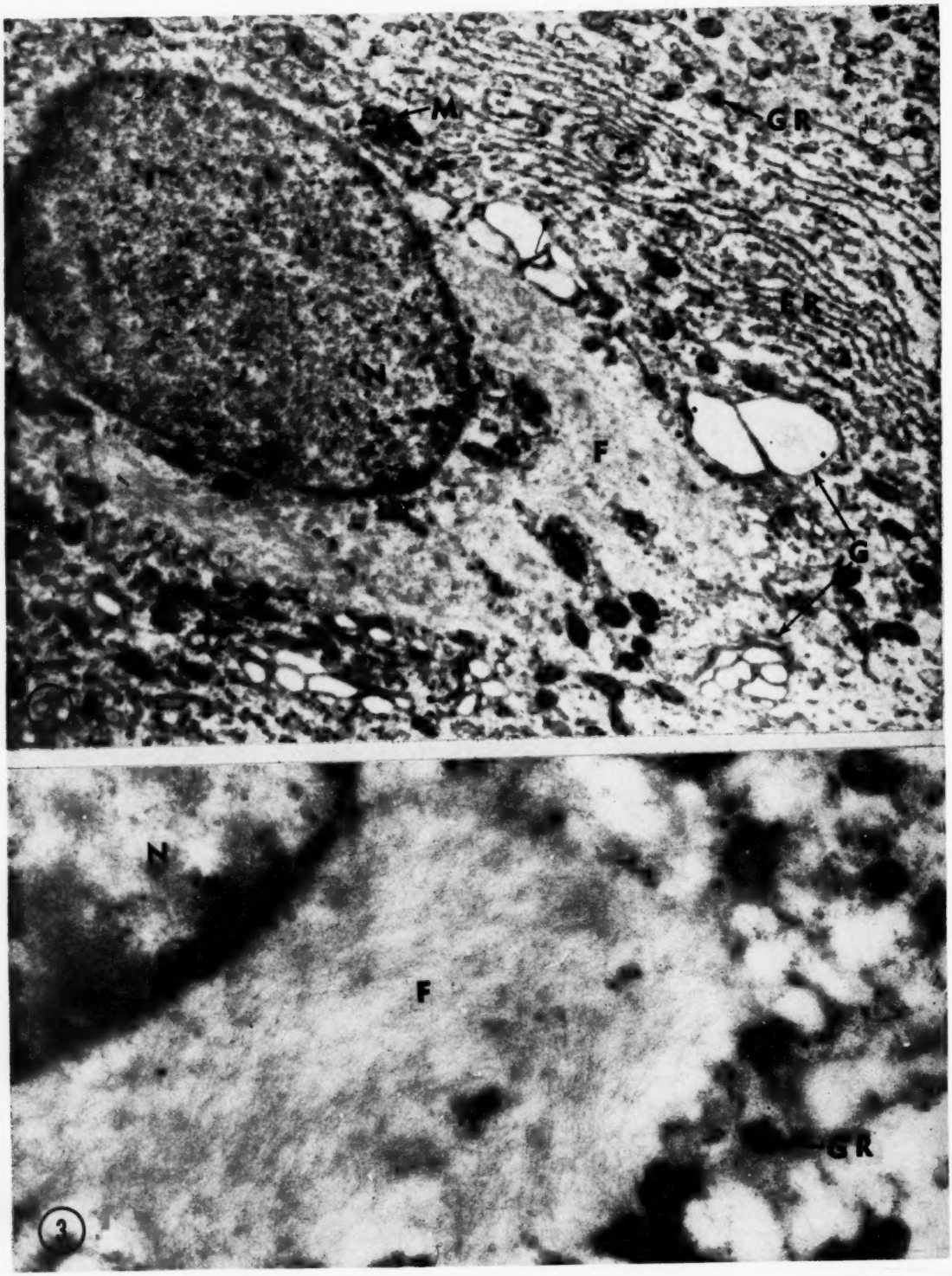

M
GR
ER
N
F
G
2
N
F
GR
3

FIG. 2. Electron micrograph of a beta cell of the rabbit. A gray, fibrillar area (F) partially surrounds the nucleus (N). The peripheral limits of the fibrillar substance are irregular. A prominent Golgi complex (G) is present around the peripheral extent of the fibrillar substance (F). The beta granules (GR) are small and are surrounded by membranes. ER—ergastoplasm; M—mitochondria. X20,700.

FIG. 3. Higher magnification of the fibrillar area (F) of a beta cell of the rabbit. The meshwork of fine fibrils adjacent to the nucleus (N) is demonstrated. A beta granule (GR) with a surrounding membrane is also shown. X41,000.

and associated small granules,[3] is scattered diffusely throughout the cytoplasm between the beta granules. The smooth membranes comprising the Golgi complex are prominent and occupy varying positions in the cytoplasm. The mitochondria are recognized easily by the presence of internal cristae.

Rabbit: Figure 2 illustrates a beta cell of the islet of a rabbit. The nuclei usually are round or ovoid and contain nucleoli. The distinguishing electron microscopic feature of the beta cells is the presence of a fine, fibrillar substance adjacent to the nucleus (figures 2 and 3). This substance partially or completely surrounds the nuclei, and is present to a varying degree in all of the beta cells of the rabbit, but was not observed in the beta cells of the other species examined. The fibrillar substance does not appear to be associated with the membranous system of the ergastoplasm, the Golgi membranes or the nuclear membranes. It extends irregularly into the surrounding cytoplasm. The Golgi complex is prominent, and partially or completely encircles the nuclei at a position approximately midway between the nuclear membranes and the plasma membranes of the beta cells. The beta granules are small and round (figure 2). Their average diameter is approximately 130 mμ. The other components of the cytoplasm are small, distinct mitochondria and an abundance of ergastoplasm. The plasma membranes are distinct and form a continuous boundary around each of the islet cells. Focal areas of increased density of the plasma membranes of adjacent islet cells are observed at irregular points. These areas of increased density probably represent terminal bars. An intercellular space is present between the terminal bars, and small, cytoplasmic projections of the islet cells protrude into this intercellular space.

Guinea pig: The nuclei of the beta cells are dense and round. The beta granules are scattered diffusely throughout the cytoplasm and between them is an abundance of ergastoplasm (figure 4). The average size of the beta granules is approximately 230 mμ. They are round or irregularly shaped (figure 4). The Golgi apparatus is prominent, and is usually found adjacent to the nuclei.

Rat: Figure 5 illustrates a beta cell of the rat pancreas. The nuclei of the beta cells are dense and round or ovoid.

The granules are round and are surrounded by a distinct membrane. Frequently, a prominent, clear space is observed between the granules and their surrounding membranes. The average diameter of the beta granules is approximately 170 mμ. The Golgi complex is prominent, and is observed in several different areas of the cytoplasm near the nuclei. The mitochondria are distinct, and are scattered throughout the cytoplasm. The cytoplasm between the granules, mitochondria and Golgi complex appears dense due to the presence of a large amount of ergastoplasm in these areas (figure 5). Terminal bars and prominent intercellular spaces containing cytoplasmic projections of the islet cells are observed (figure 5). Cross sections of these cytoplasmic projections are occasionally observed as isolated structures in the intercellular space.

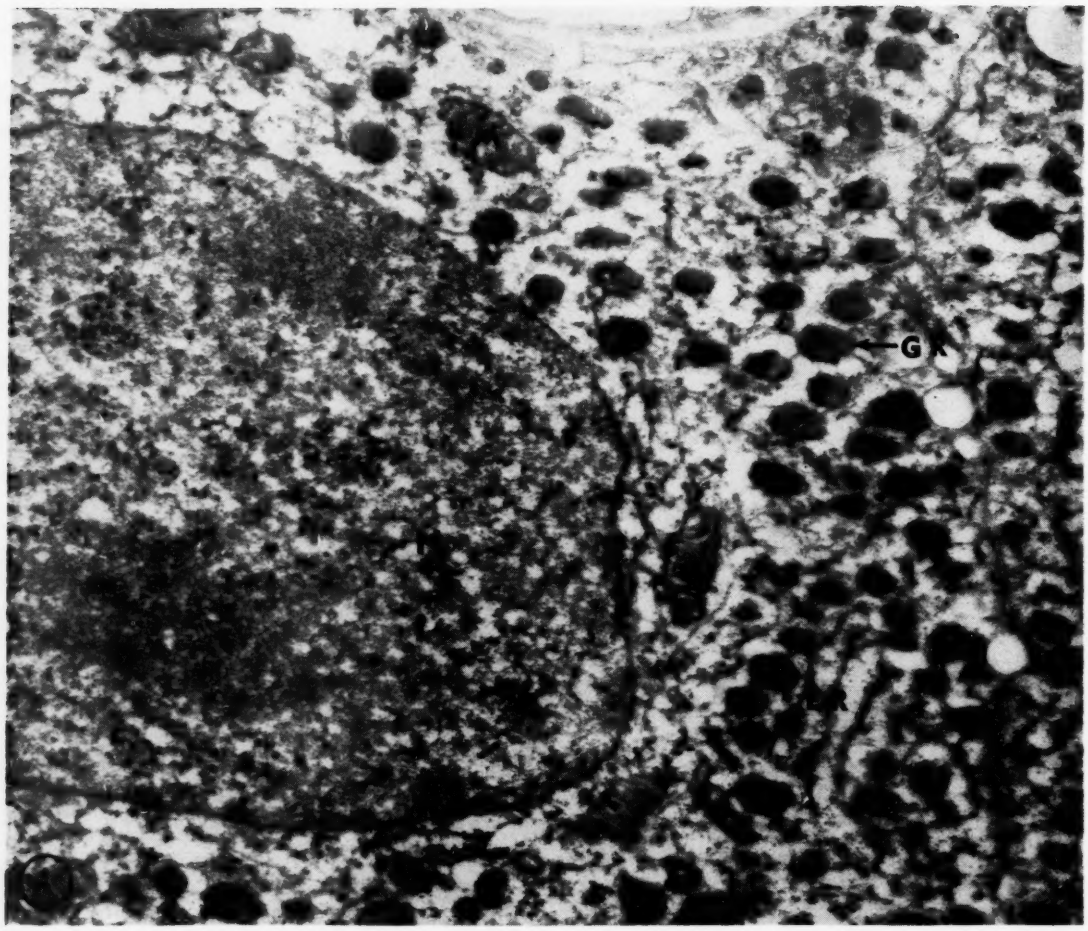
Alpha Cells

The alpha cells differed from the beta in the following general electron microscopic features: The concentration and density of the granules of the alpha cells are greater than of the beta granules; the Golgi complex is smaller, and the amount of ergastoplasm in the alpha cells is less than in the beta cells.

Dog: The contours of the nuclei of the alpha cells are irregular (figure 6). The granules are round in contrast with the rectangular granules of the beta cells (figures 6 and 1). The average diameter of the alpha cell granules is approximately 170 mμ. Dense, irregularly-shaped structures are observed occasionally in the alpha cells (figure 6). These structures are assumed to be lipid inclusions.

Rabbit: The alpha cells are packed with dense, round granules. They are larger (diameter, approximately 200 mμ) than those of the beta cells (diameter, approximately 130 mμ). The nuclei are usually ovoid.

Guinea pig: The alpha cells are recognized easily due to the presence of numerous, dense round granules in a relatively pale cytoplasm in contrast with the larger granules of the beta cells present in a dense cytoplasm. The average diameter of the alpha cell granules is approximately 180 mμ in comparison with the corresponding figure of 230 mμ for the beta granules. The difference in density of cytoplasm of the two types of cells is due mainly to a greater amount of ergastoplasm in the beta cell. The nuclei of alpha cells are pale and ovoid.



Rat. The average diameter (180 mμ) of the granules of the alpha cells is approximately the same as the average diameter (170 mμ) of the beta granules. The cytoplasm of the alpha cells appears pale, and apparently contains a lesser amount of ergastoplasm than the beta cells of the rat.

C Cells

C cells were identified in the islets of the guinea pig pancreas. Their cytoplasm appears pale and devoid of distinct granules (figure 7). The mitochondria and Golgi complex are usually indistinct in these cells, and they contain only a small amount of ergastoplasm. This type of cell was not observed in the islets of the other species of animals.

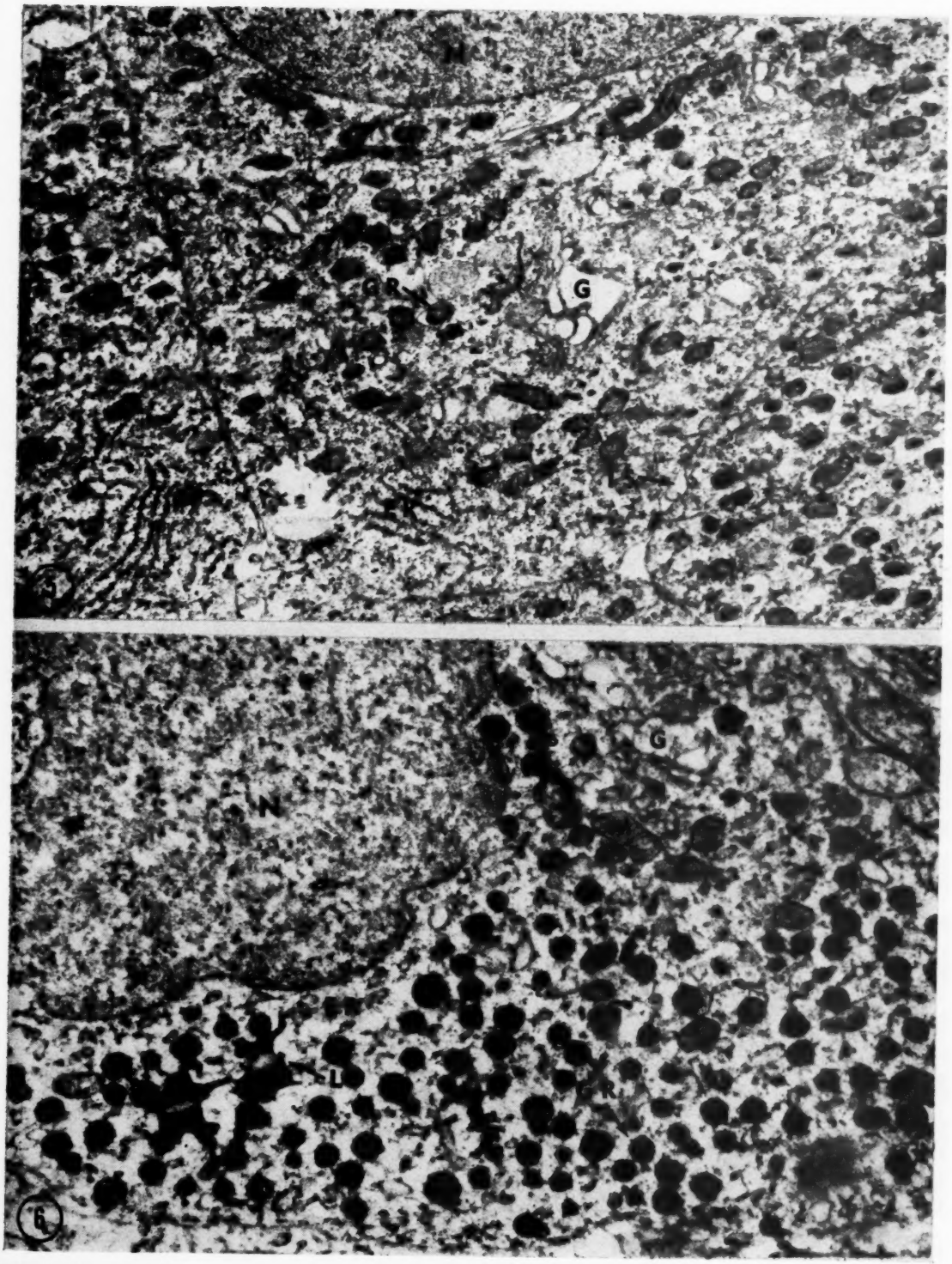
Capillaries and Nerve Fibers

A complete lining of endothelial cytoplasm is present in the capillaries. It is attenuated at focal points (figure

FIG. 4. Electron micrograph of a beta cell of the guinea pig. Large, irregularly shaped beta granules (GR) are scattered diffusely throughout the cytoplasm. Between the beta granules and mitochondria (M) is an abundance of ergastoplasm (ER). N—nucleus. X25,000.

FIG. 5. Electron micrograph of a portion of a beta cell of the rat. The beta cell in the center is separated from the surrounding beta cells by distinct plasma membranes which extend from the upper left- and upper right-hand portions of the illustration. Portions of the Golgi complex (G) can be observed in several areas in the cytoplasm. The beta granules (GR) are rounded and are surrounded by a clear space with an outer limiting membrane. The background cytoplasm appears dense due to the abundant ergastoplasm (ER). A distinct intercellular space (IS) is present in some areas. M—mitochondria, N—nucleus. X23,000.

FIG. 6. Electron micrograph of a portion of an alpha cell of the dog. The nucleus (N) has an undulating contour. The cytoplasm contains dense rounded granules (GR), a Golgi complex (G), mitochondria (M), and a small amount of ergastoplasm (ER). Irregularly shaped lipid inclusions (L) are also present. X18,800.


N
G
G
N
L
6

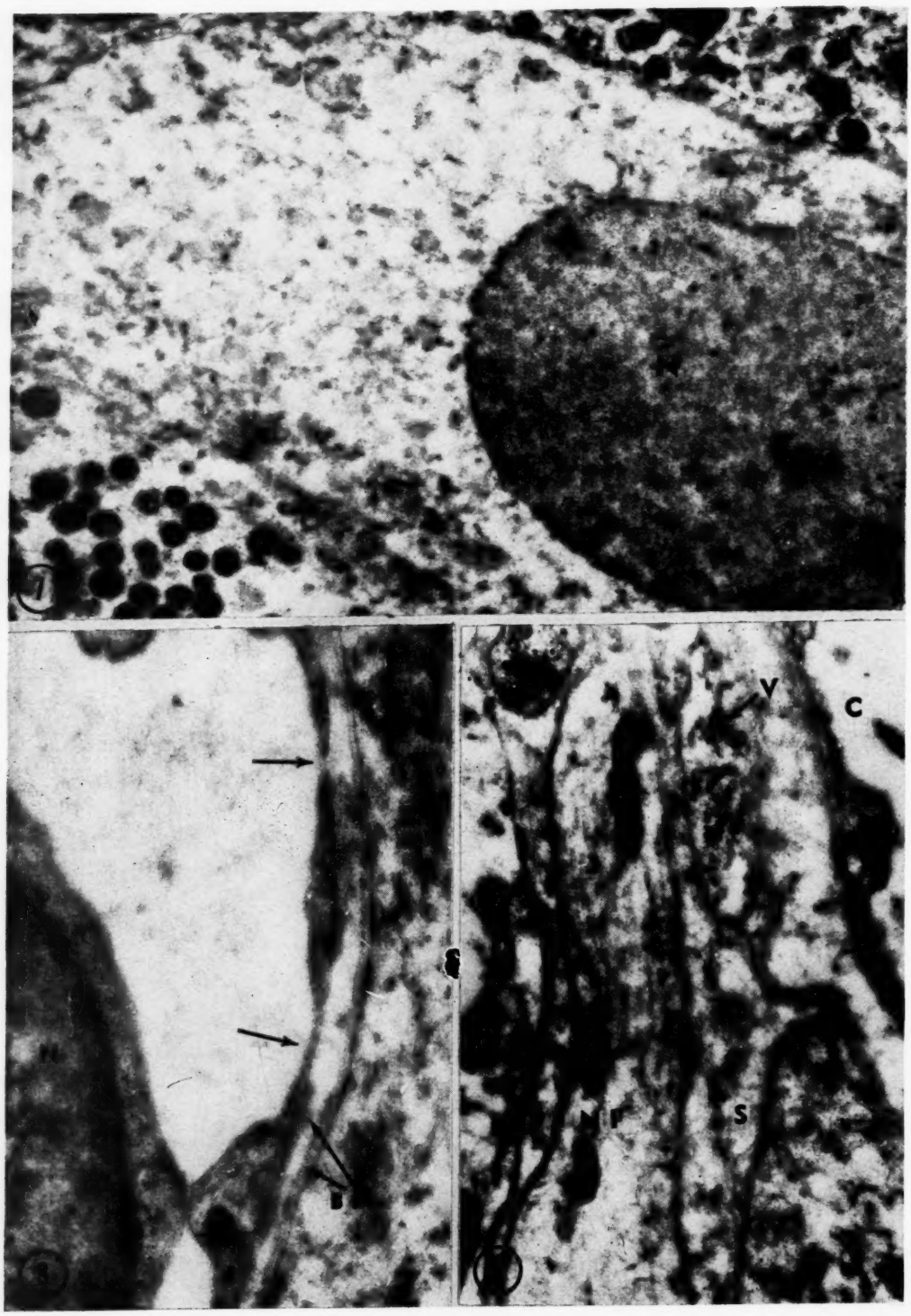

V
C
S

FIG. 7. Electron micrograph of a C cell of the guinea pig. The cytoplasm appears relatively clear and contains only a small amount of ergastoplasm without any distinct granules. Above the C cell is a portion of a beta cell and below it is a portion of an alpha cell. N—nucleus. X25,000.

FIG. 8. Electron micrograph of a portion of a capillary in an islet of Langerhans of the guinea pig. The endothelial nucleus (N) bulges into the capillary lumen. At the lower arrow, the endothelial plasma membranes are closely apposed and at the upper arrow the plasma membranes appear as a single line. The basement membrane of the endothelium and the basement membrane of the islet cell are shown. The two basement membranes appear fused in some areas. X31,000.

FIG. 9. Electron micrograph of a nerve fiber in an islet of the dog. The axoplasm of the nerve fiber (NF) appears fibrillar. The cytoplasm (S) and plasma membrane surrounding the axolemma of the nerve fiber are probably a part of a Schwann cell. A structure containing microvesicles (V) is adjacent to the basement membranes of a capillary (C). X28,400.

8) at which the plasma membranes of the endothelium are apposed and appear as one.

Two basement membranes are observed between the capillaries and the islet cells. One is a layer of moderately dense amorphous material applied to the plasma membrane of the endothelium (figure 8). The second is a similar layer of amorphous material applied to the plasma membranes of the islet cells adjacent to the capillaries (figure 8). A space is usually present between these two basement membranes, although in some instances they appear continuous. The amorphous material is present only around the capillaries, and does not extend into the intercellular spaces of the islet cells.

Unmyelinated nerve fibers are observed occasionally in the electron micrographs of the islets of Langerhans (figure 9). The nerve fibers are identified on the basis of the fibrillar appearance of the axoplasm and the presence of a surrounding sheath of Schwann cell cytoplasm (figure 9). The electron microscopic, fibrillar appearance of the axoplasm of nerve fibers has been demonstrated by Hess and Lansing.[4]

Gasser[5] has shown that the plasma membranes of the Schwann cells form a mesentery-like attachment or mesaxon, around peripheral, unmyelinated nerve fibers. The closely applied plasma membranes of the nerve fiber and the Schwann cell are illustrated in figure 9.

Palay[6] has reported the following electron microscopic features of a synapse in the central nervous system; collections of microvesicles and mitochondria in the presynaptic expansion of the nerve fiber and closely apposed limiting membranes of the presynaptic and postsynaptic cell. In one instance, a few nerve fibers in the perivascular space of an islet contain microvesicles (figure 9). These fibers could not be identified as presynaptic endings at the present time, because they are not closely apposed to the plasma membranes of either the islet cells or endothelial cells, and they do not contain clusters of mitochondria. Unmyelinated nerve fibers closely applied to the plasma membrane of an alpha cell were observed in the dog pancreas. The investing Schwann cell cytoplasm and its plasma membrane were present only on the outer portion of the nerve fibers, and were not present between the plasma membranes of the alpha cell and the nerve fiber. They could not be identified as presynaptic endings, since clusters of mitochondria and microvesicles were not observed in these fibers.

DISCUSSION

The rectangular profile of beta granules in the dog is an unusual and unexpected observation. Our initial reaction was that this appearance was an artifact, but the beta granules were found to be rectangular, when the dog pancreas was fixed in either osmic acid buffered to different *p*H values or in 10 per cent formalin. Rectangular granules were not observed in the beta cells of the other species of animals examined, even though the same methods of fixation, dehydration and embedding were used in all instances. On the basis of these findings, we believe that the rectangular profile of the beta granules in the dog pancreas is not an artifact in the usual sense of the term.

The rectangular granules in the beta cells of the dog probably represent cross-sections of a disc or plate. This three-dimensional form of the granules seems most probable, since the granules with rectangular profiles usually extend completely across the clear spaces, and only a few spaces are devoid of granules. This concept of a single plate or disc does not apply to all of the granules, since some appear in the form of a V or T and as round granules in the electron micrographs. It is unknown at the present time why the beta granules of the dog have this unusual appearance. It may be that the granules are compressed into flattened discs or plates by fluid accumulating in the sacs surrounding the individual granules, or they may represent a crystalline form of insulin or insulin-precursor. Other explanations may become apparent, when these cells are studied under experimental conditions producing increased secretory activity of the beta cells.

Distinct differences in the ultra structure of the beta cells of the dog, rabbit, guinea pig and rat were observed (figures 1, 2, 4 and 5). Since the beta granules apparently represent insulin or an insulin precursor,[7] the rectangular profiles of canine beta granules may indicate a

species-difference in endogenous insulin or insulin-precursor. Immunologic differences between the endogenous insulin of guinea pigs and mice have been demonstrated by Moloney and Coval.[8] Preliminary studies in this laboratory on the demonstration of insulin in the beta cells of different species of animals by the fluorescent antibody technic also have indicated immunologic differences in endogenous insulin.[9]

The composition and functional significance of the fine, fibrillar substance which partially or completely surrounds the nuclei of the beta cells of the rabbit (figures 2 and 3) is unknown at the present time. Thomas[10] described a homogeneous area at one side of the nuclei of the beta cells of the elasmobranchii. This area has been called a macula or macular zone.[10, 11] Bencosme[11] described a similar zone near the nuclei of alpha and beta cells of the rabbit, and demonstrated that the macular zone was distinct from the Golgi complex. The fibrillar substance, which is observed by electron microscopy in the beta cells of the rabbit, may correspond to this macular zone, although there is no electron microscopic evidence of a fibrillar area in the alpha cells of the rabbit.

Unmyelinated nerve fibers are observed within the islets of Langerhans and are identified on the basis of their structure. Nerve fibers and the termination of these fibers on the islet cells have been demonstrated by light microscopy.[12, 13] Definite electron microscopic evidence of synaptic terminations of nerve fibers within the islets has not been obtained as yet. The presence of microvesicles in some of the nerve fibers is suggestive that these fibers are presynaptic, but the other electron microscopic criteria for synapses[6] is not present.

Cytoplasmic projections in the space between the islet cells indicate that it is a true space and not an artifact. Secretory products of the islet cells could enter the capillaries either through this space and across the basement membranes around the capillaries, or directly through the portion of the cells attached to the basement membranes.

SUMMARY

The normal electron microscopic structure of the islets of Langerhans of the dog, rabbit, guinea pig and rat has been studied. Distinct differences in the electron microscopic structure of the beta cells are present in each of the species of animals. The majority of the beta granules of the dog pancreas have a rectangular profile in contrast to round beta granules in the other species of animals. A fine, fibrillar substance surrounds, partially or completely, the nuclei of the beta cells of the rabbit. This fibrillar material apparently is not associated with the nuclear membranes, Golgi membranes or the ergastoplasm. The alpha cells differ from the beta cells in the following general electron microscopic features: The concentration and density of the granules of the alpha cells are greater than the beta granules; the Golgi complex is smaller, and the amount of ergastoplasm is less than in the beta cells. Unmyelinated nerve fibers are present in the perivascular space within the islets of Langerhans. The endothelial cytoplasm is markedly attenuated at focal areas. In these areas of attenuation, the endothelial, plasma membranes are apposed and appear as a single line. Distinct intercellular spaces are present between the islet cells.

SUMMARIO IN INTERLINGUA

Studios per Microscopia Electronic in Re le Structura de Normal Insulas de Langerhans in Canes, Conilios, Porcos de India, e Rattos

Esseva studiate per microscopia electronic le structura normal del insulas de Langerhans in canes, conilios, porcos de India, e rattos. Distincte differentias structural del cellulas beta es constatabile per microscopia electronic inter omne le species individual. Le majoritate del granulos beta in le pancreas canin ha un profilo rectangular, per contrasto con le ronde granulos in le altere species. Un fin substantia fibrillar investi partial- o completemente le nucleos del cellulas beta de conilios. Iste substantia fibrillar es apparentemente non associate con le membranas nucleari, le membranas de Golgi, o le ergastoplasma. Le cellulas alpha differe ab le cellulas beta in le sequente aspectos general in tanto que illos se revela sub le microscopio electronic: Le concentration e le densitate del granulos del cellulas alpha es plus grande que illos del cellulas beta. Le complexo de Golgi e le quantitate de ergastoplasma del cellulas beta es plus grande que illos del cellulas alpha. Nonmyelinate fibras nervose es presente in le spatio perivascular intra le insulas de Langerhans. Le cytoplasma endothelial es marcatemente attenuate in areas focal. In iste areas de attenuation, le membranas de plasma endothelial es apponite e se presenta como un sol linea. Distincte spatios intercellular es presente inter le cellulas del insulas.

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The Support of Biological Research

The age of a research laboratory can be measured in many ways. Chronological age is not only important for the record but it is also important for its effect upon program. A research organization over the years develops both a personality and a reputation and these affect the morale, the work output, and the type and caliber of men that can be recruited. Inevitably, therefore, the age of a research organization has effects which arise from traditions and the evolution of its program. There is another kind of aging in research laboratories, however, that is more important than chronological age and this is the aging of ideas. In some areas of research it is most desirable that a man devote his entire career to a relatively narrow field. This may be the only way in which the work can be most productive and the field effectively explored. This kind of aging is good. It is maturity rather than aging, but ideas, like men, tend to become senile after they have matured and sometimes the work can become ineffective just because the ideas are worn out by old age. On the other hand, some laboratories are still in their early youth and a visit with the staff gives one a feeling of the vitality of a youthful laboratory. Vitality in a research laboratory is an elusive thing to define but to me vitality in a laboratory is much more meaningful than any attempt to measure research productivity. Vitality, elusive though this may be, is something that can be sensed in a laboratory. There is an intellectual verve in the staff — a thing that Alan Gregg has so aptly termed "the climate of expectancy." It is an air of adventure, of optimism, and of enthusiasm. . . .

And now I want to say a few words about industrial support of biological research. While support by the federal government has increased enormously during the last 20 years, support by industry has also increased considerably and today industry — largely the pharmaceutical industry — conducts about 30% of the nation's total medical research and their research expenditures rose from $25 million in 1941 to $60 million in 1952, including $3 million given to universities and medical schools. Most business men today realize that support of research is not only good business but is necessary for staying in business at all. It must be recognized too that the pharmaceutical industry's primary job is to make and market useful products from the results of basic research. Industry now also recognizes another responsibility, and that is to assist basic research so that there will continue to be new findings on which to base new products. The importance of this may be appreciated from the statement made by a representative of a pharmaceutical house that 60% of the drugs sold today did not exist 10 years ago and 90% of the prescriptions now written by doctors could not have been filled 15 years ago.

From "The Support of Biological Research," by W. H. Sebrell, Jr., in *American Scientist* 2:150 and 153, March 1957.

Urinary Excretion Patterns of Some B-Vitamins in Diabetes

A Study in Patients with and without Degenerative Complications

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Abnormalities in the metabolism of some of the B vitamins have been suggested as occurring in patients with diabetes mellitus.[1, 2] Furthermore, the similarity of the peripheral neuropathy associated with diabetes to that seen in certain vitamin deficiencies has also been cited as evidence for altered vitamin utilization in diabetics.[3, 4] However, the prolonged use of large amounts of the various B vitamins, especially thiamine and B_{12}, in the treatment of diabetic neuropathy has usually been without beneficial effect, and consequently has led to some doubt concerning the rôle of vitamin deficiencies as an etiologic factor.[5, 6] Improvement in carbohydrate tolerance and decreased insulin requirement have also been reported in diabetic patients following the administration of thiamine and other B vitamins, as well as ascorbic acid.[7]

A recent study reported a striking difference in the response to a test dose of vitamin B_{12} between diabetic patients with and without retinopathy.[8] Whereas those with retinopathy excreted approximately 40 per cent of a 50 mcgm. test dose, patients without this complication excreted only 10 per cent of it. However, this could not be confirmed by another group of investigators who found no difference between diabetic patients with or without retinopathy.[9]

Lossy, Goldsmith and Sarett observed that diabetic subjects excreted twice as much of a 5 mg. test dose of thiamine as did nondiabetics.[1] Although eleven of twenty-three diabetics had clinical evidence suggestive of vitamin complex deficiency, there was no difference in their test dose response as compared to the other twelve diabetics. In contrast, Pollack et al. found no difference between a large group of diabetic patients and normals following a 1 mg. test dose although 9 per cent of the diabetics had excretion values suggestive of thiamine deficiency.[10] Using larger test doses (50 to 100 mg.), Alexander noted reduced excretion of thiamine in diabetic as compared to normal persons.[11] The phosphorylation of thiamine by liver slices from diabetic animals has also been studied. Foa et al. observed that the total thiamine content of such liver slices was normal, but the amount of thiamine pyrophosphate was greatly reduced.[12] Insulin restored the thiamine pyrophosphate levels of the liver slices from diabetic animals back toward normal. Siliprandi et al. were unable to confirm the effect of insulin but did find decreased thiamine pyrophosphate in tissues from alloxan diabetic rats.[13]

Increased excretion of a test dose of riboflavin by diabetics has also been reported.[1, 14] In one of these studies, the increase was correlated with negative nitrogen balance, and was also seen in nondiabetics during such periods.[14] Charalampous and Hegsted have reported an impaired ability to acetylate sulfadiazine in diabetic rats, but did not indicate whether this was due to a pantothenic acid deficiency or a failure to convert pantothenic acid to acetyl coenzyme A.[15] However, Maengwyn-Davies et al. found that diabetic patients acetylated more of a test dose of sulfadiazine than did normals, but there was no difference between patients with and without retinopathy.[16] These workers had also observed that the reduced eosinopenic response to adrenocorticotropin in diabetics without retinopathy could be restored to normal by large doses of panto-

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thenic acid.[17] Pantothenic acid deficiency is known to produce adrenal cortical insufficiency, although in humans there has been no evidence of any consistent change in the glucose tolerance test.[18] Reduced excretion of a test dose of niacin by diabetics has been reported by Lossy et al., but in a later study there was no difference between the diabetics and normals.[1, 19]

The present study was undertaken in an attempt to resolve some of the conflicting results which have been obtained in relationship to the metabolism of several of the B vitamins in diabetes. In none of the previous studies were the patients placed on a standardized dietary regime to minimize the effects of previous diet prior to the administration of the test dose of vitamins. In general, no attempt had been made to divide the diabetic patients into those with degenerative complications and those without, nor had the relationship between the control of the diabetes and the response to the test dose of vitamins been given adequate consideration. In this study attempts have been made to control these factors.

METHODS

All individuals studied were males between the ages of twenty and forty-nine years. None of them exhibited any clinical evidence of vitamin deficiencies. They were divided into three groups of seven in each group: 1. normal controls with no demonstrable disease; 2. diabetic patients with no evidence of retinopathy, neuropathy, or nephropathy; 3. diabetic patients with retinopathy, neuropathy, and nephropathy. The average age of each group and the range was twenty-three (twenty to twenty-eight), thirty-five (twenty to forty-nine) and thirty-four (twenty-one to forty-two) respectively. In addition to a history and physical examination, the diabetic patients were evaluated by the following procedures: Ophthalmologic and neurologic examinations, chest X ray, electrocardiogram, X-ray examination of the legs for vascular calcification, blood urea nitrogen, PSP excretion test, endogenous creatinine clearance and urinalysis. The diabetic patients were given amounts of insulin necessary to maintain as good control as possible without producing frequent hypoglycemia. The majority of them represented the juvenile type of the disease and consequently diabetic control was not always ideal. Each patient was hospitalized on the metabolic ward and given a constant daily diet[20] calculated to contain 35 calories/kg. of body weight, 1.6 mg. of thiamine, 0.8 mg. of riboflavin, and 8 mg. of niacin. The pantothenic acid and vitamin B_{12} content of the diet were kept as constant as possible. The composition of the diet was 71 gm. protein, 85 gm. fat and sufficient carbohydrate to supply the remainder of the caloric intake prescribed. Insofar as possible, large amounts of staples and frozen foods were set aside at the beginning of the study to minimize the normal variation in the vitamin content of the various foods in the diet. Several different samples of the complete daily diet were also assayed for their vitamin content and were found to contain 1.8 mg. of thiamine, 1.1 mg. of riboflavin, 2.7 mg. of pantothenic acid, 11.7 mg. of niacin and 5.1 mcgm. of vitamin B_{12}. After a period of at least two weeks on this diet, each patient was given a single test dose of 5 mg. of thiamine, 5 mg. of riboflavin, 50 mg. of calcium pantothenate, 50 mg. of nicotinic acid and 50 mcgm. of vitamin B_{12} with breakfast. In preliminary studies this two-week period was found to be sufficient to eliminate the effects of previous diet. All the vitamins for the test dose were given orally except the B_{12} which was given by intramuscular injection. Following the test dose, each patient was maintained on the standard diet for another six days and then the test dose was repeated. However, in the diabetics insulin was withdrawn on the day of the second test dose and withdrawn or reduced the two days before the test dose. Since this procedure resulted in a weight loss, the normal controls were given a 525-calorie diet and restricted fluids (1,000 cc.), but with the same vitamin content, on the last three days of the study in an attempt to equal the weight loss observed in the diabetic patients. This diet consisted of 36 gm. of protein, 19 gm. of fat and 52 gm. of carbohydrate.

Twenty-four hour urine collections in brown bottles were made throughout the study. Toluene was used as a preservative, and the urine was kept refrigerated during the collection period. The completeness of the collection was ascertained by urinary creatinine determinations. Twenty-four hour urinary glucose was also measured as an indication of the adequacy of the diabetic control. The patients were weighed daily.

Aliquots of the twenty-four hour urine collections were analyzed for thiamine, riboflavin, pantothenic acid, N^1-methyl nicotinamide, and vitamin B_{12} for several days before and including the day of each test dose. Thiamine was measured by the thiochrome method.[21] Riboflavin was determined by a microbiological procedure using *lactobacillus casei* ATCC 7469.[22] *Lactobacillus arabinosus* 17-S ATCC 8014 was used as the test organism for the microbiological assay of pantothenic acid.[23] N^1-methyl nicotinamide was assayed by the procedure of Huff and Perlzweig.[24] Vitamin B_{12} was determined by the titration of lactic acid produced in the microbiological method employing *lactobacillus leichmannii*.[25]

RESULTS

The pretest dose urinary excretions of the various B vitamins during the period when the diabetes was controlled as well as possible are shown in table 1. Although both groups of diabetics excreted more thiamine than did the nondiabetics, the differences were not significant for this number of patients. For the other vitamins the differences among the various groups were even smaller. The amount of glycosuria, although comparable in the two groups of diabetics, indicates that the diabetes was not rigidly controlled. This may be partly attributed to the fact that almost all of these were "unstable" diabetics whose control had never been satisfactory.

The results following the first test dose are summarized in table 2. In each case the test dose excretion has been corrected for the average daily excretion of the vitamin just prior to the administration of the test dose. The diabetics with degenerative complications excreted significantly less niacin than did those without complications and the normals. However, the differences among the three groups in respect to the excretion of thiamine, riboflavin, pantothenic acid and vitamin B_{12} were not significant. During both the pretest and first test dose period, the patients maintained constant weight.

The second test dose was given to the diabetics after insulin therapy had been withdrawn, and consequently they were losing weight. The nondiabetics were given a restricted caloric diet and fluid intake which also resulted in a similar, but not strictly comparable, weight loss, since the factors of dehydration and tissue breakdown were not equivalent. The results, again corrected for the pretest dose excretion values, are contained in table 3. The diabetics without degenerative complications excreted more thiamine than did the other two groups following this second test dose. However, only the difference between the two diabetic groups was significant. There was also significantly greater excretion of pantothenic acid by the diabetics without complications as compared to the normals and other diabetics, while there was no difference between these latter two groups. Although there were no significant differences comparing the three groups in respect to the response to the test dose of riboflavin and niacin, it should be noted that there was an augmented excretion of these two

TABLE 1

Average daily pretest excretion values

Patient Group and (No.)		B_1 μg./day mean ± S.E.M.	Riboflavin μg./day mean ± S.E.M.	Pantothenic acid mg./day mean ± S.E.M.	Niacin mg./day mean ± S.E.M.	B_{12} μg./day mean ± S.E.M.	Glycosuria gm./day mean ± S.E.M.
Normals	(7)	287 ± 121	190 ± 38	2.11 ± 0.18	4.92 ± 0.67	0.083 ± 0.010	–
Diabetics without complications	(7)	374 ± 112	222 ± 35	2.79 ± 0.17	4.78 ± 0.62	0.081 ± 0.015	28.2 ± 11.3
Diabetics with complications	(7)	483 ± 112	173 ± 35	2.49 ± 0.17	4.07 ± 0.62	0.105 ± 0.008	29.5 ± 17.4

TABLE 2

Mean test dose excretion corrected for pretest dose values

Patient Group and (No.)		B_1 μg./day mean ± S.E.M.	Riboflavin μg./day mean ± S.E.M.	Pantothenic acid mg./day mean ± S.E.M.	Niacin mg./day mean ± S.E.M.	B_{12} μg./day mean ± S.E.M.
Normals	(7)	847 ± 101	1,673 ± 212	13.16 ± 2.15	7.10 ± 0.48	18.43 ± 3.70
Diabetics without complications	(7)	980 ± 92	1,740 ± 200	15.93 ± 1.96	7.20 ± 0.45	19.76 ± 4.23
Diabetics with complications	(7)	916 ± 94	1,586 ± 199	14.13 ± 1.79	4.99 ± 0.45*	14.34 ± 3.83

*Confidence limits for controls vs. diabetics with complications 3.54 to 0.69.
Confidence limits for diabetics without complications vs. diabetics with complications 3.58 to 0.86.

TABLE 3

Average test dose excretion during insulin deficiency corrected for pretest dose values

Patient Group and (No.)	B_1 μg./day mean ± S.E.M.	Riboflavin μg./day mean ± S.E.M.	Pantothenic acid mg./day mean ± S.E.M.	Niacin mg./day mean ± S.E.M.	B_{12} μg./day mean ± S.E.M.	Glycosuria gm./day mean ± S.E.M.	Weight loss kg. mean ± S.E.M.
Normals (7)	674 ± 120	2,122 ± 324	12.52 ± 3.39	10.20 ± 1.17	15.50 ± 5.14	–	2.15 ± 0.24
Diabetics without complications (6)	984 ± 118	2,768 ± 321	26.57 ± 3.03*	10.93 ± 1.16	18.23 ± 6.39	196 ± 57.0	1.92 ± 0.67
Diabetics with complications (5)	430 ± 131†	2,294 ± 350	14.83 ± 3.66	8.24 ± 1.24	17.06 ± 6.24	141 ± 62.6	3.00 ± 0.94

*Confidence limits for diabetics without complications vs. controls 24.03 to 4.08.
Confidence limits for diabetics without complications vs. diabetics with 21.85 to 1.64.
†Confidence limits for diabetics without complications vs. diabetics with 935 to 173.

vitamins as compared to the first test dose results. This increase tended to be greater in the diabetics than in the normal, even though the weight loss in the three groups was comparable (table 3). It is evident from the amount of glycosuria on the day of the second test dose that the diabetics were insulin deficient. Increased riboflavin excretion secondary to negative nitrogen balance has been reported.[14] The differences mentioned above in regard to thiamine and pantothenic acid are significant, whether they are corrected for pretest excretion values or those obtained from the first test dose which was given under conditions of diabetic control.

DISCUSSION

In the interpretation of the urinary excretion following a test dose of a vitamin it has usually been assumed that a decreased excretion represents a deficiency in the body stores of that vitamin. Conversely, an increased excretion indicates saturation of these stores.[1] Another interpretation of such results is possible. Increased excretion could conceivably result from impaired ability to utilize the vitamin even though a deficiency of it already existed. Many of the B vitamins in their active form exist as phosphorylated compounds. The conversion of the vitamin to its active form is an energy-consuming process involving adenosine triphosphate. If this compound were limiting, as has been postulated in diabetes,[26] it is possible that some of the vitamins could not be utilized and consequently would be excreted. The measurement of urinary excretion of vitamins does not really give any information concerning the relative importance of these two possibilities—tissue saturation or impaired utilization.

At the present time the full meaning of the decreased excretion of niacin by the diabetics with complications following the first test dose is not apparent. The fact that the excretion of the other vitamins given at the same time was normal is somewhat against the possibility of impaired absorption of niacin. Decreased renal clearance of niacin also seems unlikely in view of the normal patterns for the other vitamins and the use of twenty-four hour urine collections. Previously Lossy et al. had also found a decreased excretion of niacin in diabetics, but in a later study were unable to confirm this.[1, 19] No details were given concerning the types of diabetic patients studied in the later experiment. This seems to be important because in the present study the diabetics without complications were no different from nondiabetics, whereas it was only the diabetics with complications who had decreased niacin excretion.

During the period of uncontrolled diabetes, the diabetics without degenerative complications excreted more of the test dose of thiamine than did the other group of diabetics. The diabetics without complications also had a greater excretion of pantothenic acid than did the other two groups. Since the weight loss during this period was similar in both groups of diabetics, these differences cannot be attributed to negative nitrogen balance. If these results are a manifestation of impaired utilization of these two vitamins in this group of diabetics rather than an indication of saturated body stores, then one would still have to explain the lack of increased excretion of these vitamins in the diabetics with complications. Perhaps if this increased excretion of pantothenic acid in the uncomplicated diabetics did represent impaired utilization, it would be consistent with the ob-

servation of Becker et al. that a normal eosinopenic response to adrenocorticotropin in this class of diabetics can be restored by giving large doses of this vitamin.[17] It should also be noted that during the period of insulin deficiency riboflavin and niacin excretion were increased as compared to the levels when the diabetes was controlled. If such periods of uncontrolled diabetes persisted, serious depletion of body stores of these vitamins could result. This could explain the occasional clinical observation of the appearance of vitamin deficiencies when diabetes is controlled following a period of severe ketoacidosis or prolonged hyperglycemia and glycosuria.[5, 27, 28] Control of the diabetes with re-establishment of normal metabolic processes undoubtedly produces an increased demand for vitamins and in the face of depleted body stores, a relative vitamin deficiency could easily develop.

The relationship, if any, of these findings to the presence of diabetic complications is not clear at this time. Each patient was studied for approximately one month while it is usually a matter of years before the degenerative complications of diabetes make their appearance. These studies do not provide any basis for implicating abnormalities in the metabolism of some of the B-vitamins as etiologic factors in the degenerative lesions of diabetes, although the long-term effects of the small differences may have some importance. Even though it has not been possible to resolve many of the conflicts in the literature regarding the response of the diabetic to test doses of these vitamins, an attempt has been made to delineate more carefully the numerous variables which must be considered in any undertaking of this kind.

SUMMARY

The urinary excretion patterns of thiamine, riboflavin, pantothenic acid, niacin and vitamin B_{12} have been studied in normals, diabetics with and diabetics without degenerative complications. Each patient was given a constant standardized diet for two weeks before the administration of the first test dose to minimize the effects of previous diet. The second test dose was given six days later when insulin had been withdrawn from the diabetics and the normal controls had been given a restricted caloric diet and fluid intake. There were no significant differences in the excretion patterns among the three groups before the first test dose. The diabetics with degenerative complications excreted less of the first test dose of niacin than did the other two groups of patients. During the period of insulin deficiency the diabetics without complications excreted more of the thiamine test dose than those with complications and more of the pantothenic acid than the other two groups. The excretion of riboflavin and niacin was greater after the second test dose than after the first in all groups. This was probably a manifestation of negative nitrogen balance and weight loss.

It was not possible to determine any definite relationship between the development of the degenerative complications of diabetes and the excretion patterns of the five B-vitamins tested.

SUMMARIO IN INTERLINGUA

Excretion Urinari de Alicun Vitaminas B in Diabete: Un Studio in Patientes Con e Sin Complicationes Degenerative

Le excretion urinari de thiamina, riboflavina, acido pantothenic, niacina, e vitamina B_{12} esseva studiate in subjectos normal, in diabeticos sin complicationes degenerative, e in diabeticos con tal complicationes. Omne le subjectos recipeva constante dietas standardisate ante le administration del prime dose experimental pro reducer al minimo le effectos de previe dietas. Le secunde dose esseva administrate sex dies plus tarde, quando le diabeticos habeca cessate reciper insulina durante que le subjectos de controlo habeva comenciate reciper dietas a restriction caloric con reducite quantitates de fluido. Ante le administration del prime dose experimental, nulle significative differentias in le modos de excretion esseva notate inter le tres gruppos. Le diabeticos con complicationes degenerative excerneva minus del prime dose experimental de niacina que le altere duo gruppos. Durante le periodos de carentia de insulina, le diabeticos sin complicationes excerneva plus del dose experimental de thiamina que le diabeticos con complicationes e plus del dose experimental de acido pantothenic que le altere duo gruppos. Le excretion de riboflavina e de niacina esseva plus grande post le secunde que post le prime dose experimental in omne le gruppos. Isto esseva probabilemente un manifestation de un negative balancia de nitrogeno e de perdita de peso.

Il non esseva possibile determinar un relation definite inter le disveloppamento de complicationes degenerative in diabete e le modo excretional del cinque vitaminas B que esseva includite in le studio.

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We are indebted to Miss A. G. Sampson and her metabolic kitchen staff for the preparation of the diets. We are grateful to Drs. Olaf Mickelsen, M. R. S. Fox, and George Briggs for their interest and helpful suggestions. We should like to express appreciation to Dr. R. L. Stearman for the statistical analysis of the data.

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DISCUSSION

HENRY T. RICKETTS, M.D., (*Chicago*): I gathered that many of the complicated cases of diabetes were suffering from renal disease. Has Dr. Field any observations on the response to a test dose of B-vitamins of nondiabetic patients with other kinds of renal disease?

DR. BOGER, (*Philadelphia*): I couldn't agree more about the confusion of B_{12} in diabetes.

We have studied this problem in over 400 patients and compared to normals, the diabetics show no difference in the serum B_{12} concentrations. The uncomplicated diabetics have the same B_{12} levels as the complicated diabetics. We have found a slight but not significant difference in favor of female diabetics as opposed to males. I think the B_{12} concentration in the diabetic has been correlated in some measure with vascular systemic damage to a far greater degree than to the diabetic state itself. What studies have been made of nondiabetic patients who have as much vascular damage?

DR. DAWSON: Becker and Lang had sent us on a wild goose chase with a theory they had staked out that

vitamin B_{12} would sharply discriminate between those with and without retinal changes. There is no difference in the diabetic with or without complications, and his B_{12} excretion and the serum B_1 levels.

Recently we have found markedly elevated serum pantothenic levels in patients treated with Orinase. The explanation of this baffles us.

DR. FIELD, (*closing*): In answer to Dr. Ricketts' question, we have not studied nondiabetics with similar degrees of renal disease. We did consider the possibility that the decreased excretion of niacin might result from decreased renal function. We attempted to minimize the renal effect by collecting urine samples for twenty-four hours. The usual procedure involves collecting urine for four to eight hours, since it had been shown that the majority of the test dose would be excreted that rapidly.

One cannot generalize about the response of other vitamins from the results, but if the response that we found in respect to niacin was due primarily to decreased renal function, then one might expect decreased excretion of all other vitamins.

We were happy to hear of Dr. Boger's study. We were aware of Dr. Dolger's studies which were published in the *American Journal of Clinical Nutrition* (January, 1957).

We have no information on the observation by Dr. Boger that B_{12} levels were slightly higher in females. We purposely picked all male patients, because, as you can see, the number of variables is already large. We did not want to increase it by having sex differences.

We did not do complete liver function tests on all patients. The tests which we did and the clinical findings indicated that there were no gross abnormalities in liver function.

Insulin

Insulin, the pancreas hormone, affects protein metabolism mainly through its action on carbohydrate metabolism. In diabetes, the increased glyconeogenesis involves catabolic breakdown of body proteins, and as a consequence of the abnormal sugar utilization the protein synthesis is also disturbed. The protein "anabolic" or "negative catabolic" effect of insulin administration in diabetes is therefore evidently a consequence of improved carbohydrate utilization and of decreased glyconeogenesis. It was also observed that after insulin injection the blood amino acid concentration decreases. Furthermore, it was found that insulin increased the amino acid uptake by the isolated tissues and organs of diabetic animals. These observations do not seem to necessitate, however, the assumption that insulin has a specific effect on protein metabolism itself.

The observation of Long, Katzin and Fry that *adrenal cortical extracts* increase urinary nitrogen excretion has been confirmed not only in animal experiments but also in man. Similar observations have been made after injection of cortisone and of ACTH. In best agreement with these results it was found that the loss of cortical secretion results in a decreased urinary nitrogen output. Based on such results, cortisone and ACTH have recently been designated as "protein *catabolic* hormones."

The experiments in which the uptake of some labeled amino acids have been investigated did not contribute much to the understanding of the mechanism by which these hormones induce their catabolic effect on protein metabolism.

Besides the "catabolic," also some "anti-anabolic" effects of cortex hormones have been demonstrated. Thus, for instance, the production of connective tissue in wound healing was found to be decreased after injection of ACTH or cortisone.

According to some authors, the adrenal hormones may exert many of their effects on protein and amino acid metabolism indirectly by influencing primarily the carbohydrate metabolism. This view is supported by the finding that the negative nitrogen balance seen after injection of cortex extracts, cortisone or ACTH, can be often counteracted by increased food intake alone. Finally, we have to consider that the adrenal cortex produces many different hormones which may differ in their effect on protein metabolism. The classification of the adrenal hormones into "catabolic" and "anabolic" groups represents a rather ingenious attempt to introduce some system into this confused picture. There is no doubt, however, that all these classifications show, in Albright's expression, "a goodly sprinkling of metaphysics."

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. Philadelphia, Lea & Febiger, 1955, Chapter "Digestion, Absorption and Metabolism of Protein" by Ernest Geiger, M.D., Ph.D., p. 133.

Hyperglycemic Effect without Anabolic Effect of Beef Growth Hormone in Man

E. Rudolf Froesch, M.D., William F. Ganong, M.D., Herbert A. Selenkow, M.D., Walter Goodale, M.D., Albert E. Renold, M.D., George W. Thorn, M.D., Boston*

The biologic properties of growth hormone preparations presently available are poorly defined and vary greatly from species to species. This may result in part from more marked differences between growth hormones from various species than is the case for other protein hormones such as insulin, adrenocorticotropic or posterior pituitary hormones.[1, 2] The growth hormone preparations available in amounts sufficient for adequate testing have usually been those extracted from the pituitaries of beef and hog; they have in general been tested in rats, cats and dogs. The preparations tested have been of varying degrees of purity and have been prepared by various procedures. None has as yet been shown conclusively to be free of metabolically active contaminants.

Some of the postulated actions of growth hormone on metabolism have been summarized in figure 1. Growth hormone, by definition, stimulates growth of certain tissues, and thereby induces retention of nitrogen, potassium, calcium and phosphorus. In order to evidence an anabolic response to growth hormone it would appear that hypophysectomized animals should possess an adequate reserve of insulin in addition to being skeletally immature.[3, 4] Skeletally adult animals and those with an insufficient insulin reserve may develop hyperglycemia and transient or permanent diabetes mellitus under the prolonged influence of the hormone but fail to show evidence of tissue growth.[5, 6, 7] The production of hyperglycemia, glucosuria and sometimes permanent diabetes mellitus is the best documented and most consistent effect of relatively large doses of growth hormone on carbohydrate metabolism. Smaller doses restore normal insulin sensitivity in previously hypersensitive hypophysectomized animals.[8] The hyperglycemic effect of growth hormone has been most clearly demonstrated in cats and dogs. It has also been reported that growth hormone administered in vivo decreases the ability of muscle cells to assimilate glucose[9] and to combine chemically with insulin.[10] In addition, the rapid infusion of growth hormone has been reported to produce transient hyperglycemia and breakdown of liver glycogen, similar to that observed after administration of glucagon;[11] this has led to the postulate that growth hormone stimulates the releases of glucagon. Immediate hypoglycemic responses to growth hormone have also been noted and have been explained by some investigators as reflecting a stimulation of insulin secretion[12, 13] and by others as a peripheral insulin-like effect of growth hormone itself.[14] It should be kept in mind that the explanations for all of these activities are still hypothetical since no conclusive evidence exists to show that they are due to growth hormone and not to some other contaminating pituitary factor. Excellent recent reviews of the literature are available.[8, 15, 16]

Both beef and hog growth hormone have been administered to *human* subjects either acutely or over periods of several months,[11, 17, 18, 19, 20] and occasional anabolic responses, as judged by nitrogen, potassium, calcium and phosphorus retention, have been observed. However, no convincing growth response has as yet been obtained. Although, during growth hormone ad-

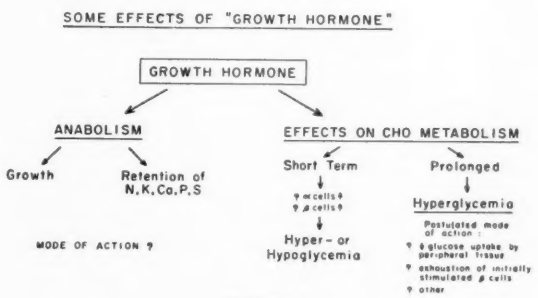


FIGURE 1

From the Departments of Medicine, Harvard Medical School, and the Peter Bent Brigham Hospital, Boston, Massachusetts.

* Recipient of a Fellowship from the American Diabetes Association.

ministration, isolated episodes of accelerated growth have been recorded, the interpretation of these observations is difficult since spontaneous growth also occurred in all of these patients. On the other hand, a definite decrease in glucose tolerance and the development of glucosuria has been observed in two of the six patients treated by Shorr,[18] while impairment of diabetic control during short courses of growth hormone administration to diabetic patients has also been reported.[19, 20] These results in man are somewhat at variance with the results obtained in other primates, since beef growth hormone is without effect in rhesus monkeys, either on growth or on glucose tolerance.[2, 21]

The ideal patients in whom to assess the value of currently available growth hormone preparations are hypopituitary dwarfs with immature epiphyses and well-documented arrest of growth. The authors have had the opportunity of carrying out prolonged administration of beef growth hormone to such a patient, as well as that of administering growth hormone over a shorter period of time to an hypophysectomized diabetic subject. The results of these studies form the basis for this report.

MATERIALS AND METHODS

The growth hormone preparation used was a highly purified preparation (D 728076) from beef pituitaries supplied by Dr. E. Fullgrabe of Armour and Company and assayed by the rat growth test. Other pituitary tropic hormones had been assayed for and were reported as "less than 50 milliunits" per mg. adrenocorticotrophin and 0.06 units per mg. thyrotropin. Further evidence for lack of significant quantities of adrenocorticotrophin was obtained by assays in hypophysectomized dogs whose adrenal veins had been previously cannulated, according to the procedure of Nelson and Hume.[22] These assays were carried out in collaboration with Dr. John E. Bethune and indicated a contamination of the growth hormone preparation with somewhat less than 2 milliunits of adrenocorticotrophin per 100 mg. The total daily dose of adrenocorticotrophin given in this study therefore did not exceed 3 milliunits.

The thyrotropin used was Armour Thytropar. One U.S.P. unit of this preparation represents the activity of 20 mg. of the preparation in tablets of the U.S.P. reference substance. The metabolic studies were carried out in the metabolic unit of the Peter Bent Brigham Hospital. Urinary 17-hydroxycorticoids were measured by the method of Reddy;[23] blood and urine glucose was measured enzymatically by the method of Froesch and Renold.[24]

OBSERVATIONS ON A PATIENT WITH HYPOPITUITARY DWARFISM

Case report. Patient N.S., a sixteen-year-old female, had a a normal birth, infancy and early childhood. At the age of eight she experienced several convulsive seizures as well as episodes of loss of consciousness and hyperpyrexia. At that time she was already one of the smallest girls in her class. Two years later, at the age of ten, the occurrence of coma, fever and vomiting along with the roentgenographic finding of suprasellar calcification led to the diagnosis of craniopharyngioma. A suprasellar cyst was aspirated by Dr. Donald H. Matson at the Children's Medical Center in Boston, resulting in complete relief of the intracranial symptoms. From the age of eight, and continuing after operation the patient gradually developed the signs and symptoms of hypopituitarism. By the age of sixteen years no further skeletal development had taken place. Maturation persisted at the level of a normal eight-year-old child and her height remained constant around 129 cm. Serial height measurements have been recorded for the last five years. The development of secondary female sex characteristics did not progress beyond the prepubertal stage. Hypoadrenocorticism was suggested by hypotension and hyperpyrexia during stressful episodes, and was established by the response to ACTH. Adrenal replacement therapy was instituted. The persistent occurrence of episodes interpreted as morning hypoglycemia during the year preceding the present admission led to an increase of cortisone dosage to the relatively high level of 37.5 mg. daily. Thyroid replacement therapy was indicated by clinical symptomatology suggestive of mild hypothyroidism and by improvement following therapy. It should be pointed out, however, that despite consistently depressed basal metabolic rate (around -20 per cent on either weight or body surface basis) I^{131} uptake and protein-bound iodine were within normal limits. This suggests some residual pituitary function with respect to thyrotropin activity.

In January 1955 the patient was admitted to the metabolic ward for growth hormone administration. The roentgenogram of her hand and wrist compared with that of a normal fifteen-year-old girl is presented in figure 2. The study was outlined

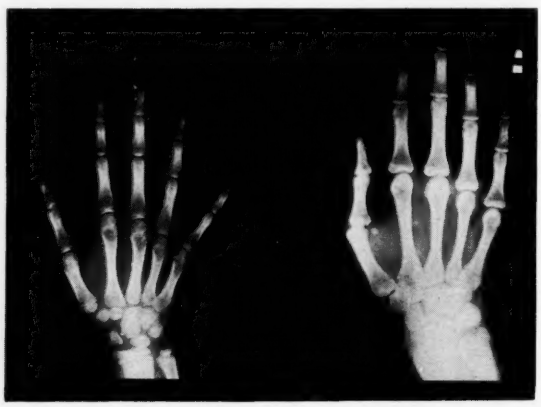


FIG. 2. Roentgenogram of patient's right hand (left) compared with that of a normal fifteen-year-old girl (right).

as follows: 150 mg. of growth hormone was administered in two daily intramuscular doses of 75 mg. each for six months. After the first month of growth hormone therapy small doses of other anabolic hormones were added to this regimen in order to achieve the best possible hormonal environment for growth hormone action. This adjunctive therapy consisted of 15 units of crystalline zinc insulin daily given in three doses of 5 units each before meals, 25 mcgm. 3,5,3′ -l-tri-iodothyronine daily, 0.2 mg. estradiol every other day, and 50 mg. of testosterone cyclopentylpropionate monthly. Cortisone was continued throughout at the previous level of 37.5 mg. daily. This adjunctive regimen was maintained for five months. Whenever changes in the hormonal treatment were undertaken, the patient was admitted to the metabolic ward and placed on a constant regimen.

Observations. No significant growth resulted from the treatment with growth hormone alone or combined with other anabolic hormones, as illustrated in figure 3. In 1951 the patient's height was recorded at 127 cm. Between 1952 and 1955 the height measurements were consistently around 129.5 cm. During the six months on growth hormone therapy her height was repeatedly measured at around 130 cm. In June 1955, one single recording of 134.5 cm. was made. This recording is out of line and probably erroneous. The patient's weight showed no consistent changes during hormone therapy and there was no roentgenographic evidence of skeletal maturation.

HEIGHT AND WEIGHT MEASUREMENTS OBTAINED OVER A PERIOD OF FIVE YEARS IN A HYPOPITUITARY DWARF

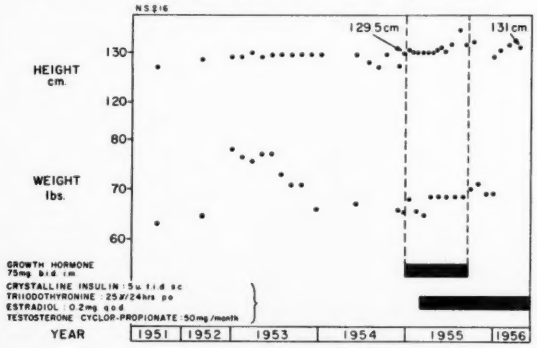


FIGURE 3

In accord with the failure of growth hormone to stimulate growth the metabolic indices did not suggest strikingly increased anabolism (figure 4). No significant changes occurred in the urinary excretion of nitrogen, calcium, potassium, phosphate or creatinine. The lower levels of nitrogen excretion during the second and third balance period are the result of decreased dietary protein, imposed by the patient's inability to continue on the previous protein intake. Blood urea nitrogen values appeared to be somewhat depressed during growth hormone therapy. The half life of infused I^{131} labeled albumin was 11.5 days before treatment and 10.2 days starting on the seventh day of treatment, an insignificant change.

The only definite immediate metabolic response to growth hormone was a small but significant rise of urinary true glucose from control levels of 100 mg. to 400 mg. on the fifth day (figure 4). Thereafter urinary glucose excretion gradually returned to the control level. It should be recalled that urinary glucose was enzymatically measured and that the normal excretion of glucose in the urine under these conditions does not exceed 250 mg. per day. Some initial elevation of the fasting blood glucose from 55 to 85 mg. per cent was also observed. There was no change in the urinary excretion of 17-hydroxycorticoids and 17-ketosteroids during the period of growth hormone administration. Indication of a more protracted activity of this growth hormone preparation on carbohydrate metabolism was obtained three days after discontinuation of growth hormone, during which time the administration of the other hormones was continued. At that time, the patient experienced a severe hypoglycemic reaction which recurred after intravenous glucose therapy, the blood glucose falling to 30 mg. per cent. During the previous five months, while receiving growth hormone and insulin, and while maintained on the same dietary regimen, the patient had not experienced any hypoglycemic reactions. After this incident insulin therapy was omitted.

Contamination of this growth hormone preparation by thyrotropic hormone was substantiated by the production of significant increases in various parameters of thyroid function during growth hormone therapy (figure 5). The initially low basal metabolic rate of minus 25 per cent rose to plus 15 per cent after one month of treatment, the twenty-four-hour I^{131} uptake rose from 50 per cent to 75 per cent and the serum protein-bound iodine increased from 3.5 mcgm. to 10.0 mcgm. per cent. During the third month of treatment, however, all three indices returned to pretreatment level and below, suggesting the possibility of antibody formation and resulting acquired resistance to exogenous thyrotropin. The addition of 25 mcgm. of l-tri-iodothyronine may have partially contributed to further suppression of residual endogenous thyrotropin secretion. However, this dosage of l-tri-iodothyronine is insufficient to accomplish complete suppression of endogenous TSH production, and its inhibitory effects on thyroid function are, under such circumstances, easily overcome by exogenous thyrotropin administration.

A further effect of growth hormone administration in this patient is illustrated in figure 6. Urinary excretion of uropepsin rose from 1,300 to 4,500 units per day on the third day of growth hormone therapy, then slowly returned to pretreatment levels. This cannot be accounted for on the basis of increased adrenal function since adrenocorticotrophin contamination of the growth hormone preparation used has been adequately excluded and since no measurable increase occurred in the urinary excretion of 17-hydroxycorticoids.

OBSERVATIONS ON A HYPOPHYSECTOMIZED PATIENT WITH DIABETES MELLITUS

Although the study reported above suggested the presence of hyperglycemic activity in the beef growth hormone preparation used, the magnitude of the metabolic effects produced did not appear to warrant a definitive conclusion. However, the hyperglycemic activity of this preparation was unequivocally confirmed in a subsequent study carried out in an adult patient with diabetes

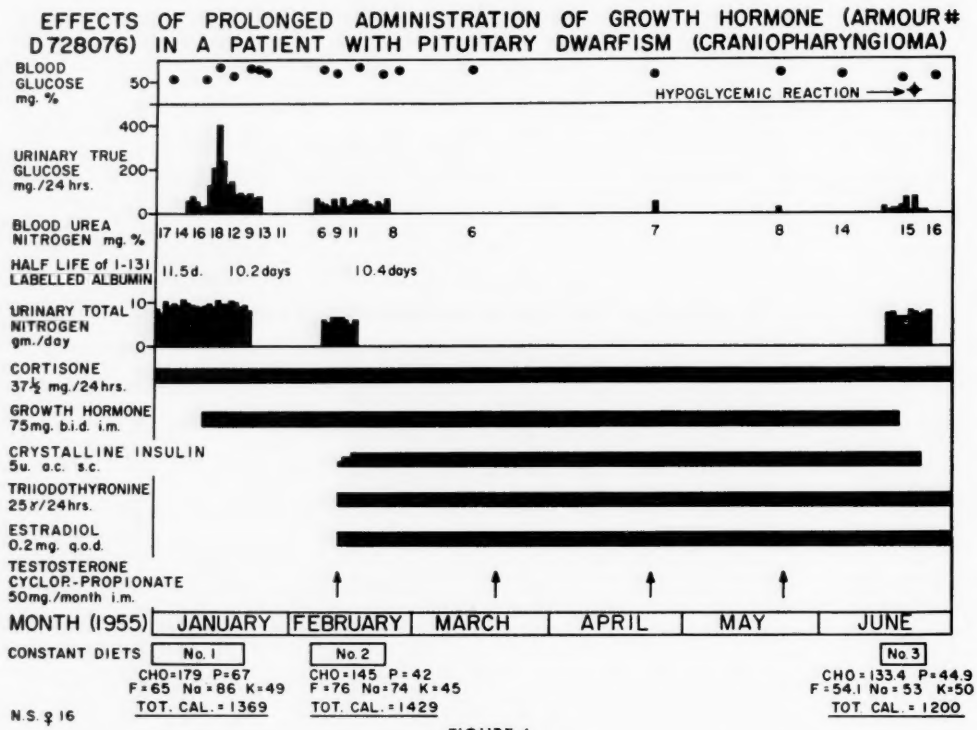


FIGURE 4

EFFECTS OF PROLONGED ADMINISTRATION OF GROWTH HORMONE (ARMOUR #D728076) IN A PATIENT WITH PITUITARY DWARFISM (CRANIOPHARYNGIOMA)

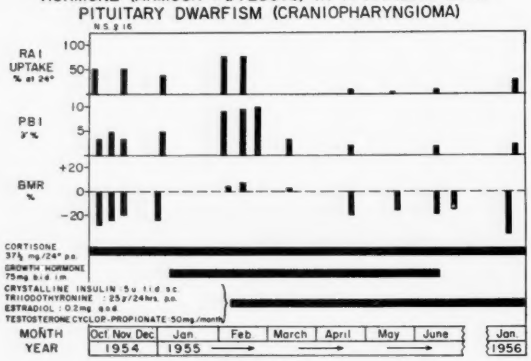


FIGURE 5

EFFECT OF GROWTH HORMONE (ARMOUR #D728076) ON THE URINARY EXCRETION OF UROPEPSIN IN A 16 YEAR OLD PITUITARY DWARF

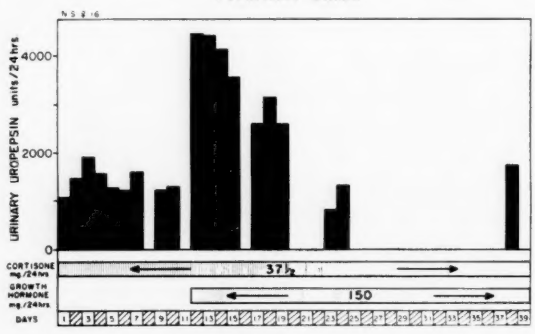


FIGURE 6

mellitus who had undergone hypophysectomy three months previously.

Patient M.G., a forty-four-year-old male executive, had been known to have diabetes mellitus for five years. Reasonable control could be achieved with 35 to 45 units of NPH insulin daily. One year prior to admission the patient developed a rapidly progressive diabetic retinopathy with numerous microaneurysms, hemorrhages and exudates. Renal function was well maintained. Because of the relentless progression of the retinal changes, hypophysectomy was performed by Dr. Donald H. Matson three months before the present study. The early postoperative course was complicated by several generalized convulsions and an extensive hemorrhage into the vitreous of the left eye. Retinal examinations were difficult, but failed to reveal any significant change. The insulin requirement decreased to 8 units of NPH insulin daily on a dietary regimen similar to the preoperative one. A functionally complete hypophysectomy was further suggested by the development of hypothyroidism and by a marked decrease in urinary steroid excretion. It seemed important to establish the nature of the markedly de-

creased insulin requirement, and accordingly the following study was carried out.

The patient was placed on a constant regimen; insulin was withheld throughout. Maintenance therapy consisted of 60 mg. desiccated thyroid and 37.5 mg. of cortisone daily. To prepare for a possible untoward reaction the cortisone dose was increased to 75 and 50 mg. on the first and second day of the administration of growth hormone. Growth hormone, 75 mg., was administered intramuscularly twice daily for a period of four days. Six days after discontinuation of growth hormone administration cortisone was again increased to 75 and 50 mg. but without concomitant growth hormone. Furthermore, since definite stimulation of thyroid function resulted from the thyrotropic hormone contained in the growth hormone, a second control study was indicated. Thyrotropic hormone (Armour Thytropar), at a dose level estimated to be equivalent to that contained in the growth hormone preparation (5 units twice daily), was administered intramuscularly for five days and cortisone again increased to 75 mg. and 50 mg. on the first and second days of thyrotropin administration.

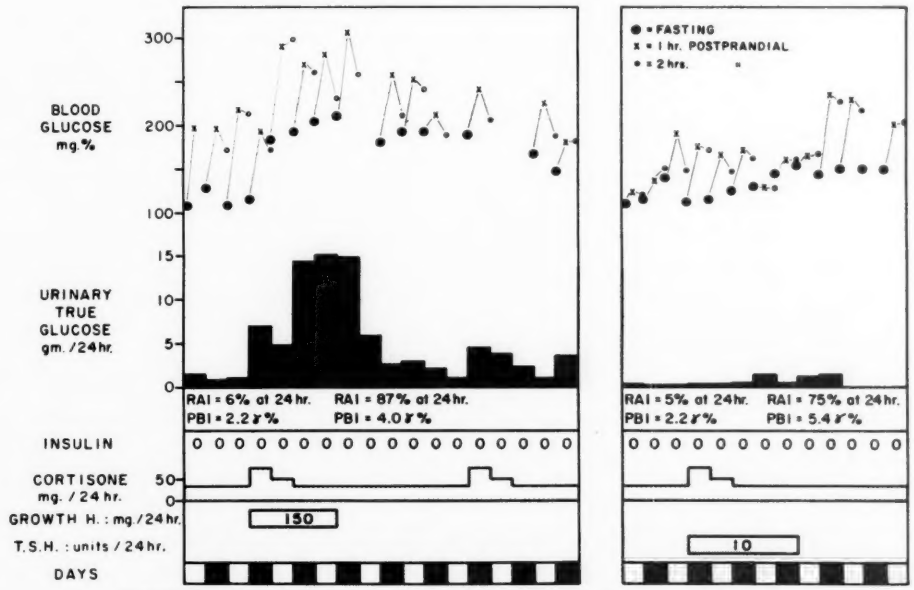
The positive findings of this study are summarized in figure 7. During the control period, while the patient was on a constant diet, the daily urinary glucose excretion varied between 0.5 and 1.5 gm. On the first day of growth hormone the urinary glucose rose to 7 gm. and was 5 gm. on the second day. Glucosuria then increased to a maximum of 15 gm. and remained elevated for two days after discontinuation of growth hormone. Concurrent with the increased glucosuria, fasting blood glucose levels increased markedly from about 100 to about 200 mg. per cent and postprandial blood glucose values were correspondingly elevated. The twenty-four-hour I^{131} uptake rose from 6 to 87 per cent on the fourth day, the serum protein-bound iodine from 2.2 to 4.0 mcgm. per cent.

When cortisone was increased to 75 and 50 mg. daily without the addition of growth hormone, only a small initial increase in urinary glucose to 4.5 gm. was noted on the first day. On thyrotropic hormone in addition to cortisone, urinary glucose excretion did not exceed 1.5 gm. It should be noted that the changes in I^{131} uptake and in protein-bound iodine, brought about by thyrotropin administration, were almost identical with those previously produced by the thyrotropin-contaminated growth hormone. The changes in blood glucose levels, observed during the control studies with cortisone alone and with cortisone plus thyrotropin, were considerably less than those previously observed during growth hormone therapy. Throughout the entire study no significant changes in urinary excretion of total nitrogen, calcium, phosphorus, potassium or sodium were noted. Body temperature and heart rate remained unaltered throughout.

DISCUSSION

To date no conclusive evidence for growth-promoting activity of available beef and hog growth hormone preparations has been obtained in man. In this study

EFFECT OF GROWTH HORMONE (ARMOUR #D728076) IN A HYPOPHYSECTOMIZED PATIENT WITH DIABETES MELLITUS



CONSTANT DIET: CHO = 186 Prot. = 84 Fat = 82 Na = 104 K = 92 Total Calories = 1819

NO SIGNIFICANT CHANGE IN THE URINARY EXCRETION OF TOTAL N, Na, K, PO_4, 17-OH, 17-K, ALDOSTERONE

M.G. 8 44

FIGURE 7

further attempts have failed to demonstrate growth-promoting activity of beef growth hormone in man under conditions believed to be ideal for growth. These conditions should be analyzed once more. The patient selected was a hypopituitary dwarf with long-standing documented arrest of growth and wide open epiphyses (bone age of eight years, chronological age sixteen). The growth hormone preparation administered was a particularly active one by animal assay, and it was administered without interruption for the relatively long period of six months and at the relatively high dose level of 150 mg. per day, in two daily doses. In order to provide the best possible hormonal environment, small doses of other anabolic hormones such as insulin, tri-iodothyronine, estradiol, and testosterone were added after an initial period of one month on growth hormone alone. No evidence of growth or increased anabolism could be detected. One possible unfavorable factor should be pointed out. The patient was maintained throughout on the relatively large dose of 37.5 mg. of cortisone daily; however, the patient never exhibited any signs or symptoms of cortisone overdosage.

The additional small doses of other anabolic hormones did not alter the response to growth hormone and failed to produce growth by themselves. It is interesting to note that 15 units of crystalline insulin per day over a period of five months did not stimulate the patient's appetite and did not result in any appreciable weight gain. Also, the small dose of testosterone which this patient received (50 mg. testosterone cyclopentylpropionate once monthly, i.e., about 1.7 mg. per day) failed to result in either growth or accelerated maturation. Sobel and Talbot[25] have recently reported that growth was stimulated maximally by 5 mg. of testosterone daily in children of small stature but without endocrine anomalies. The minimal effective dose of testosterone with relation to growth has not been established but it would appear that the dose of testosterone administered to this patient was smaller than the minimal effective dose, as had been hypothecated when the study was planned.

The lack of demonstrable anabolic activity of this beef growth hormone preparation in man contrasts with its well substantiated hyperglycemic activity. In both patients growth hormone brought about an increase in urinary glucose excretion. In patient N. S. this increase was small and derives its significance from the specific, enzymatic method used[24] and from the large number of control determinations carried out. Urinary glucose excretion in this patient had been determined during fifty control days, while on different diets, and was never found to exceed 100 mg. Two days after growth hormone treatment had been initiated urinary glucose excretion increased gradually to a maximum of 400 mg. on the fourth day, then gradually returned to control levels. Urinary glucose excretion has been enzymatically measured in well over two thousand twenty-four-hour urine collections in this laboratory and has been found, in normal subjects, to be relatively constant from day to day, not to exceed 250 mg. daily and to be almost completely independent of reasonable variations in the dietary intake of carbohydrate. On the other hand highly significant changes in this parameter have been observed consistently following the administration of carbohydrate-active adrenal cortical steroids. The response to growth hormone in patient N. S. resembles in part that which follows repeated doses of glucocorticoids, but differs in that the response to glucocorticoids is usually maximal on the first day, and in that urinary glucose excretion returns to control levels by the second or third day of glucocorticoid administration. In addition to these initial changes in urinary glucose excretion it is of considerable interest that patient N. S. experienced a severe hypoglycemic reaction to 5 units of crystalline insulin given before breakfast two days after cessation of growth hormone administration, even though she had previously tolerated without any difficulty the same insulin dose on the same diet during five months while receiving growth hormone. This suggests strongly that an effect of growth hormone on carbohydrate metabolism was present throughout the six months' period of growth hormone administration, and that resistance to this aspect of the biological activity of the preparation had not occurred.

The immediate hyperglycemic effect of the preparation used was more striking in patient M. G. and, in addition, a significant contribution of the contaminating thyrotropin to the effects on carbohydrate metabolism was adequately ruled out in this patient. Although thyroid activity was stimulated in a quantitatively equivalent fashion by the growth hormone preparation and by purified thyrotropin, the latter did not appreciably change the urinary excretion of glucose or the fasting blood glucose levels. The exacerbation of postprandial hyperglycemia which occurred two and three days after discontinuation of thyrotropin is in accord with the known action of thyroxine on glucose absorption, and with the usual lag between thyroid administration and its physiologic effects.

It would seem reasonable to conclude from these

observations that the beef growth hormone preparation used exhibited definite carbohydrate activity in man, and that this activity appeared to persist throughout a six-month period of administration to a hypopituitary dwarf. Despite this evidence for continued metabolic activity of the growth hormone preparation used, it failed to induce growth or a significant anabolic response. It would appear that, although purified preparations of beef growth hormone have been shown to exert both growth and hyperglycemic activities in animals such as toads, rats, cats and dogs, neither growth nor hyperglycemic activity can be demonstrated in rhesus monkeys, and only diabetogenic activity has as yet been demonstrated in man. This last observation can possibly be interpreted as indicating a dissociation between the anabolic and the carbohydrate effects of beef growth hormone in man. In view of the small number of patients studied to date, these conclusions must be considered as tentative.

SUMMARY

A purified preparation of beef growth hormone has been administered in two daily doses of 75 mg., each over a period of six months, to a hypopituitary dwarf with well-documented arrest of growth and wide-open epiphyses. After the first month of growth hormone therapy, small doses of insulin, tri-iodothyronine, estradiol and testosterone were added to the therapeutic regimen in the hope of achieving the best possible hormonal environment for growth hormone action. This second regimen was maintained for five months. No significant growth resulted from treatment with growth hormone whether alone or combined with other anabolic hormones. Similarly, no significant change indicative of anabolic activity was noted in the metabolic indices measured. However, mild hyperglycemic activity of the beef growth hormone preparation was suggested by small but significant changes in urinary glucose excretion and by suddenly increased insulin sensitivity after cessation of growth hormone therapy.

The hyperglycemic activity of the preparation used could be confirmed in a second study, carried out in an adult patient with diabetes mellitus who had undergone hypophysectomy three months previously. Administration of the beef growth hormone preparation resulted in a marked exacerbation of glucosuria as well as fasting and postprandial hyperglycemia. Although the preparation used was contaminated by thyrotropin, a significant contribution of this hormone to the effects of the preparation on carbohydrate metabolism was adequately ruled out in this patient. The preparation was not significantly contaminated by corticotrophin activity.

These results indicate that with respect to carbohydrate metabolism, the beef growth hormone preparation used in this study was active in *man*. The failure to detect anabolic effects of this preparation can possibly be interpreted as suggesting a dissociation between the anabolic and the carbohydrate effects of beef growth hormone in man.

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SUMMARIO IN INTERLINGUA

Effecto Hyperglycemic Sin Effecto Anabolic, Producite in Humanos per Hormon de Crescentia Bovin

Un purificate preparato de hormon de crescentia bovin esseva administrate in duo doses diurne de 75 mg durante sex menses a un nano hypopituitari con ben documentate arresto de crescentia e grandemente aperite epiphyses. Post un mense del therapia a hormon de crescentia, parve doses de insulina, tri-iodothyronina, estradiol, e testosterona esseva addite al regime in le spero de generar le melior ambiente hormonal possibile pro le action del hormon de crescentia. Iste secunde regime esseva mantenite durante cinque menses. Nulle significative grado de crescentia resultava ab le tractamento con hormon de crescentia, tanto quando isto esseva administrate sol como etiam quando illo esseva combinate con altere hormones anabolic. Similemente, nulle effecto significative de un genere indicante activitate anabolic esseva notate in le indices metabolic in tanto que istos esseva mesurate. Tamen, leve grados de activitate hyperglycemic exercite per le preparato de hormon de crescentia pareva esser demonstrate in parve sed significative alterationes del excretion urinari de glucosa e in le augmento abrupte del sensibilitate a insulina post le cessation del therapia a hormon de crescentia.

Le activitate hyperglycemic del preparato poteva esser confirmate in un secunde studio, effectuate in un patiente adulte con diabete mellite qui habeva essite subjicite tres menses previemente a hypophysectomia. Le administration del hormon de crescentia bovin resultava in un marcate exacerbation del glycosuria e etiam del hyperglycemia in stato jejun e postprandial. Ben que le preparato usate esseva contaminate per thyrotropina, un contribution significative de iste hormon al effectos del preparato super le metabolismo de hydrato de carbon esseva

excludite de maniera adequate in iste patiente. Le preparato non esseva contaminate significativemente per activitate de corticotrophina.

Le resultatos indica que con respecto al metabolismo de hydrato de carbon, le preparato de hormon de crescentia bovin usate in iste studio esseva active in le *homine*. Le facto que nulle effectos anabolic del preparato esseva detegite indica possibilemente que le effectos anabolic e le effectos super le metabolismo de hydrato de carbon que es producite per hormon de crescentia bovin in humanos es dissociate.

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SPECIAL ARTICLE

Pregnancy and Diabetes

Panel Discussion

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Moderator

William P. Given, M.D.
New York City

Priscilla White, M.D.
Boston

Edmund L. Shlevin, M.D.
New York City

Hugh L. C. Wilkerson, M.D.
Boston

MODERATOR PALMER: Ladies and gentlemen, our panel is delighted to see that there are so many doctors interested in pregnant diabetic women. I will give a brief outline of the agenda which we hope to follow. During the first part of this hour, three minutes will be allotted for each panelist to "free lance" on a phase of this subject in which he is particularly interested. The second part will be given to discussion of a hypothetical patient by two or more members of the panel; the data of this patient will be projected on the screen.

Hypothetical Patient No. 1:

Pregnant diabetic, age twenty-four years. Duration of diabetes, ten years. Primipara, grade II retinopathy. Urine albumin one on basis of three. Blood pressure 150/95.

The third part will be given to a second hypothetical patient, somewhat different, with discussion by the panelists.

Hypothetical Patient No. 2:

Pregnant diabetic, age twenty-six years. Duration of diabetes, fifteen years. Primipara, grade II retinopathy. Urine albumin one on basis of three. Blood pressure 150/100. Course average to thirty-second week on low salt diet, no gross edema, weight gain 12 lbs. During next two weeks urine albumin increased to two, blood pressure 165/100, weight increase 8 lbs., pitting edema, hydramnios, Grade II.

Presented at the Seventeenth Annual Meeting of the American Diabetes Association in New York City on June 2, 1957.

The two hypothetical patients have been chosen to represent problems with which the members of our audience are frequently confronted.

The fourth part will be allotted as follows: Each member of the panel will be given two minutes to summarize very briefly another phase of this subject in which he is interested. We will try to allow about half of this last part to questions from the audience.

Diabetic women continue to become pregnant, probably with increasing frequency. The numerous and various facets of the problem created when a diabetic woman becomes pregnant have received considerable study, but many phases remain controversial and unsolved. By way of over-all knowledge, we are making progress. Some of you may consider the subject somewhat trite. However, this morning we will attempt to present the subject of pregnancy in the diabetic in as informative and educational manner as possible.

I will first call upon Dr. White to discuss "The Natural Course of Pregnancy in the Presence of Diabetes."

DR. WHITE: Thank you, Dr. Palmer. The rather infrequent occurrence of pregnancy in the diabetic, one per 1,000 cases, has led some workers in the field to stress that sterility may be a major problem. This low incidence is due to the peculiar age behavior of diabetes. Fertility rather than sterility is today a major problem, as shown by the increased frequency with which young women with diabetic nephropathy are entering our obstetrical series. Fertility is further suggested by certain statistics, namely, the greater than average size of families in the prediabetic state, and the fact that young

women who subsequently develop diabetes have the earliest known age for onset of the menarche.

Whenever there is a problem of increased fertility, there is always a problem of increased fetal wastage. If I were asked to summarize the natural course of pregnancy in diabetes with a single word, it would be the word "destruction," shown decisively in the pre-insulin era when these women died undelivered. Today it is destruction in part, for with insulin, diabetic women survive. But if a nonintervention, and I believe nonspecific, program is followed, only one diabetic woman out of every three ends with a surviving infant. Thus the perinatal loss is 45 per cent, previable losses 20 per cent. The incidence of toxemia is 33 per cent, and to some degree, hydramnios is present in every obstetrical diabetic patient.

It is, therefore, natural to seek explanations for the causes of abnormalities, and modes for their prevention in three areas—maternal, placental and fetal structures. Abnormalities which are chemical, functional and structural occur in all three and may be correlated with fetal fatalities.

MODERATOR PALMER: Dr. Shlevin will speak next. His subject is "The Significance of Glycosuria and the Abnormal Glucose Tolerance Curve During Pregnancy."

DR. SHLEVIN: Abundant evidence has been steadily accumulating to show that diabetes may start long before clinical recognition, and that the fetal mortality in the unrecognized diabetic may be as great, if not greater, than in the known diabetic. Retrospective studies indicate that unexplained intra-uterine deaths, large-sized babies, episodes of pre-eclampsia, and even habitual abortions, may be due to diabetes lurking in the background.

This emphasizes the importance of studies in carbohydrate metabolism, particularly where there is a family history of diabetes, a poor obstetrical history, or glycosuria during pregnancy. The finding of sugar in the urine during pregnancy should be considered as due to diabetes until proved to the contrary. This statement holds, notwithstanding the fact that in at least 10 per cent or more of nondiabetic normal pregnant patients, there may be glycosuria at some time or other during the period of gestation, and that in the great majority of these, this is due to a lowered renal threshold. However, by following this principle, diabetes may be picked up earlier, and with proper management the expectation of an improvement in fetal salvage is possible.

In studying carbohydrate metabolism, postprandial blood sugars and urines are better diagnostics than fasting samples. In doubtful cases, a glucose tolerance test should be performed. Where the results are still equivocal, these tests may have to be repeated during each trimester of pregnancy, in order to track down diabetes.

Of what significance is the abnormal glucose tolerance curve during pregnancy? Is it merely an aberration of normal carbohydrate tolerance, or is it due to diabetes? Many internists and obstetricians consider this innocuous. They either exclude such cases from their published series, or treat them in the same manner as nondiabetics. Terms such as prediabetic, glucose tolerance test diabetic, latent diabetic, potential diabetic, and others have been used to apply to these cases. This, perhaps, has done more harm than good by throwing us out of focus regarding the proper principles of management of the unrecognized diabetic.

An abnormal glucose tolerance test during pregnancy is indicative of diabetes. Some of the cases may show hyperglycemia, which is transient, and may revert to normal, after the stress of pregnancy has been removed. In others, the hyperglycemia may persist, indicating diabetes. In those cases where sooner or later with the passage of time and with additional stresses the hyperglycemia reverts to normal, one can anticipate diabetes in the near or distant future in the great majority. At any rate, an abnormal glucose tolerance curve during pregnancy should not be considered innocuous, and if the same principles as in the management of the frank diabetic were applied to the unrecognized case, the results would be better, and we would have an improved fetal survival.

MODERATOR PALMER: Thank you, Dr. Shlevin. The third speaker on the panel will be Dr. Given.

DR. GIVEN: I should like to report on the management of two groups of patients and indicate the results obtained. Both of these groups were patients treated at the New York Lying-In Hospital. The first group of 131 patients was treated between 1931 and 1948. These patients were treated like any other normal pregnant women. They were allowed to go to term. Most were permitted to deliver vaginally, and the babies were cared for in the normal nursery. When reviewing these patients, we were appalled to find a total fetal loss of 34 per cent and a fetal loss of 21 per cent of babies weighing over 1,500 gm. In view of all the work being done, it seemed obvious to us that if we managed these patients very carefully, as will be outlined in a moment, we should at least halve this loss.

From 1948 through 1955, we had 113 patients. Two of us saw these patients every week. The diabetes was controlled very carefully, and, in general, acidosis was eliminated. Hospitalization was used frequently, and by

routine almost all of the patients were hospitalized after the thirtieth week and cared for in the accepted manner for hypertension, toxemia, et cetera. Delivery was prematurely induced if the patient developed hydramnios, progression of hypertension, and revealed severe toxemia, or if she had been very difficult to manage. This was done in an effort to avoid intra-uterine fetal death. Cesarean section was used on 53 per cent of the patients, in an effort to avoid traumatic death, which accounted before for about one-third of the deaths. All the babies were sent to the premature nursery and given the very best care possible for premature infants.

It should seem obvious that such care should at least halve the rate of fetal death. However, the total fetal loss rose from 34 to 36.5 per cent, and the fetal loss of infants over 1,500 gm. was the same in each group.

This very discouraging fact led us to an analysis of the facts. Obviously the first point is that, whenever prematurity is introduced as a method of treatment in any obstetrical problem, one will never get better results. This has been universally true. The second more fundamental problem is that no effort was made to alter the disease complex. We were simply trying to get the babies out alive, and were hoping that our pediatric colleagues could keep them alive. But for the fundamental lack of understanding of these babies, the pediatricians' efforts were not successful. The only trend observed was the disappearance of intra-uterine fetal death and a rise in neonatal death. We feel, therefore, that the expectant treatment at this moment is a failure.

I would like to make one comment on where we intend to go from here. Since we have not been able to approach Dr. White's results, it is perfectly obvious that we should seriously consider hormone replacement therapy. Despite the fact that in the literature no one has confirmed her work, it is very important to emphasize that no one has adequately repeated her work exactly as she has done it. We do not believe that such a fundamental piece of work could be dismissed unless one repeats it in every detail.

MODERATOR PALMER: Thank you, Dr. Given. The fourth speaker in this first part of the panel is Dr. Wilkerson. Dr. Wilkerson will speak on the subject, "The Significance of Abnormal Carbohydrate Metabolism in Pregnancy with Results to Date."

DR. WILKERSON: Dr. Shlevin has given you the important points of a theory on which we have attempted to base a clinical study. We have two main objectives: to determine first, if through the use of insulin and diet we may be able to reduce fetal wastage in certain cases of transitory abnormal carbohydrate metabolism in pregnancy; and secondly, if by the same method we ultimately may be able to prevent or delay the development of frank diabetes mellitus in both mother and child.

Our criteria for abnormal carbohydrate metabolism, set up in collaboration with a group of consultants, were based on a standard three-hour 100-gm. oral glucose tolerance test. The venous blood true glucose levels, which we consider indicative of an abnormality, are 110 fasting, 170 at one hour, 120 at two hours, and 110 at three hours. If any two of these four true glucose levels are equalled or exceeded, the woman is considered to be abnormal, so far as her ability to metabolize carbohydrate is concerned.

The results of screening tests and glucose tolerance tests are based on over 10,000 pregnancies. About 4,000 of them, or 40 per cent, were positive as shown by (1) a screening blood sugar of 130 mg. per 100 ml. or more, regardless of pregnancy or family histories; (2) positive pregnancy history—a history of a baby weighing nine pounds or more at birth, or any of the following in two or more pregnancies: fetal death, neonatal death, congenital anomaly, premature birth, toxemia; (3) family history of diabetes.

Glucose tolerance tests were done on about 3,500 of these 4,000 positive screenees, with about 6 per cent of the 3,500 giving abnormal glucose tolerance curves by our criteria. Actually, 3.5 per cent of the total women screened were considered to have positive glucose tolerance tests.

Beginning in December 1956, we attempted to do a glucose tolerance test in each trimester of pregnancy on every pregnant woman registered in the Boston City Hospital Prenatal Clinic. We have done glucose tolerance tests on 387 women who screened negative, and who up to that time would not have been given a glucose tolerance test by our routine methods. Of these, seven, or 1.8 per cent, were found to be positive.

Some results are available now in the four groups, the first three being the large and important groups—the normal or negative controls, the abnormals treated with insulin, and the abnormals not treated. The outcome of pregnancy was normal in about 80 per cent of our negative cases, in 79 per cent, or actually about the same percentage, of the women who were abnormal but corrected with insulin, but in only 68 per cent of those abnormal and not corrected with insulin injections. We mean by abnormal outcome of pregnancy—live, but weighing nine pounds or more at birth, live with a congenital anomaly, live but premature, fetal death and/or neonatal death. The only statistically significant difference between these groups is the birth weight of the children. Four times as

many children with birth weights of nine pounds and over were born to those cases with abnormal metabolism not corrected by insulin, than were born to either of the other two groups of normals and treated cases.

I might make a brief statement to the effect that we are now studying with paper chromatography the urinary findings in these women, and discover that, although 68 per cent of them had positive Benedict's tests for glycosuria after 50 gm. of glucose, only a small percentage had true glucose in the urine after food, according to paper chromatography. Much of the glycosuria by Benedict's test was apparently lactose.

MODERATOR PALMER: Thank you, Dr. Wilkerson. There may be some comments that various members of the panel have to make concerning the statements of other members of the panel; but we will defer them to the fourth part, and if they choose then to spend most of their allotted time in discussing other panelists' remarks, instead of the assigned subjects, they may do so.

The second part of the program is allotted to a discussion of hypothetical patient number one, and Dr. White and Dr. Given will be asked to comment on this patient; and if Dr. Shlevin, as time permits, has something to say, we will be glad to hear from him. Dr. Wilkerson tells me he does not care at this time to comment on these hypothetical cases.

Hypothetical Patient No. 1:

Pregnant diabetic, age twenty-four years. Duration of diabetes, ten years. Primipara, grade II retinopathy, urine albumin one on basis of three. Blood pressure 150/95.

DR. WHITE: This is a very interesting patient, Dr. Palmer. I am not quite sure of the significance of the albumin. I myself think in terms of quantitative albumin tests, but for the sake of argument I will say that it is significant, some 50 mg. or more, so that this patient would be classified as belonging to our F group. If this is not significant, it would be our D classification. If we saw this patient in the first trimester, there would be no question of interrupting the pregnancy. We would not quite but almost guarantee her survival. However, if the albuminuria is significant, the chance for fetal survival is only 50 per cent with the best possible treatment available; if the albumin is not significant, then it is nearer to 75 per cent. With the present management, her vascular status would certainly not worsen and would perhaps be improved.

In the first trimester this patient would, as her prescription for diet, receive 30 calories per kilogram of body weight. We would hope to keep her gain in weight below 15 lbs., so that the total caloric increase would not be more than 200 to 300 calories, the carbohydrate 200, and the protein a gram and a half per kilogram, with sodium restricted to one gram daily. She would receive a mixture of regular and NPH insulin, but by the third trimester I would expect that she might be on a split dose schedule. Diuretics, either ammonium chloride or possibly potassium chloride, with or without Diamox, and eventually mercurials, would be prescribed. This patient would be given our maximum dose of female sex hormonal therapy which, in 1957, is a weekly injection of Delalutin and Delestrogen, starting with 1 cc. of each per week, and for this severe case ending with nearer to 15 cc. per week. We may be overtreating these patients with this dose level. The patient would be hospitalized in the thirty-third week, and if everything had gone along well, although we would consider delivery at the end of week thirty-five, we would, if possible, edge it into week thirty-six. She would be given a trial of pelvic delivery, unless there was a breech presentation.

If I saw this patient for the first time in the second trimester, the general management would be about the same. I might be somewhat concerned, because the blood pressure was rather high, and by this time we normally would have expected it to drop a little.

If I saw the patient for the first time in the third trimester, I would not think it was too bad. The management again would be as outlined. Probably we would give this patient, even as late as this, female sex hormonal therapy, although the point could be debated, and this time, unless there were clinical reasons for not doing so, we would definitely aim for the thirty-sixth week for delivery. Again an effort would be made to induce this patient, and if she failed after twelve hours of labor, cesarean section would be done.

On the whole, this is rather a bad patient, for her vascular lesions are marked for the relatively short period of the duration of her disease, ten years.

MODERATOR PALMER: Thank you, Dr. White. Dr. Given will now comment on this patient, and as Dr. White has done, will emphasize what his attitude would be in each of the trimesters.

DR. GIVEN: Our treatment would pretty much follow what Dr. White has stated with exception of the hormones, but there are some very important points regarding this patient which I would like to emphasize.

Usually this patient arrives with the great fear that she should not be pregnant, because she has been told that she should never have become so. This we hear all the time, and I think it should be emphasized that practically there are no diabetic women who could not undertake a pregnancy. The pregnancy will practically never

cause the mother's death, despite the fact that there may be a large fetal loss.

I thoroughly agree with Dr. White that we would not interrupt this patient. As a matter of fact, we have done no therapeutic abortions whatsoever. Our rationale has been as follows: If you do an abortion, you have a 100 per cent chance of losing the baby. If you allow the patient to go to term, there is at least a chance that you may get a baby; and as far as our experience has been concerned, there has been no permanent damage to the mother. Therefore, we have not done therapeutic abortions on any diabetics.

The management of this patient is difficult, because of the various ways in which she may react. In the first trimester, we see the patients weekly. We control their diabetes by the clinical method, by seeing them each week, discussing their symptoms and watching their weight and presence of acetone in the urine, and we adjust the insulin requirement for the following week. One rarely finds any difficulty in the first trimester. The second trimester, in any pregnant woman with hypertension, whether she be diabetic or not, is the trimester in which to make a prognosis as to the outcome. There is, as you know, a physiological drop in the blood pressure in the second trimester of pregnancy. If a patient has known hypertension and does not sustain a slight drop in the second trimester, one may predict with some accuracy that her chances of having a superimposition of toxemia or a marked progression of hypertension in the third trimester may be close to 75 per cent. The second point of prognostic value in the second trimester is the increase of the amount of albuminuria. This is a very bad prognostic sign for patient and baby. A third sign of prognostic value is the progression of changes in the fundus of the eye. A fourth one would be the development of nitrogen retention. Each week, at the visit, blood is drawn for the necessary chemical analyses.

We would routinely hospitalize this patient at about thirty weeks, and from then on the treatment must depend very much on what the patient does. Very much has been said about the large baby in diabetes, and far too little emphasis has been placed on the fact that many of these babies are frightfully small. The patient with vascular disease may have a very tiny baby. A case in point was a woman, a little sicker than this one, who was hospitalized for her entire pregnancy with severe hypertension, eye ground lesions, and four-plus albuminuria. I delivered her at thirty-six weeks, because of a premature separation of the placenta, and four weeks from term the baby weighed 790 gm.

We talk so much about the happy thirty-sixth week, but we see much trouble so early. If hypertension progresses, or eye ground lesions progress, they always seem to happen at about thirty-two weeks. We are confronted with this problem of progression of hypertension or toxemia, conditions which may kill the baby, and yet we have a tiny little baby to deliver. If we leave the baby in the uterus, we may well lose it before delivery; if we deliver it, there is a very good chance that it will die in the nursery. I know of no easy way to make this decision. We like to try to carry the patient as far as possible, but when hydramnios develops, or progression of hypertension, or toxemia, I think that the baby is sicker the longer it stays in the uterus, and that it has a better chance of living in the incubator.

If we are confronted with none of these complications, hydramnios, toxemia, et cetera, we would let the patient go to thirty-seven weeks, and deliver her vaginally, if the cervix is favorable. We would do a cesarean section if she had a long, closed cervix, which is likely at thirty-seven weeks. On the other hand, if we are in trouble at thirty-four weeks, we have gone ahead and delivered the patients. The babies all have been sent to the premature nursery.

MODERATOR PALMER: Thank you, Dr. Given. I would like to comment about this early and prolonged hospitalization. How much do the economics of this problem restrict this to the very wealthy and the very poor? In the West, where we deal mostly with the intermediate economic situation, to hospitalize a pregnant girl five or six weeks before she is delivered would create in many instances an impossible problem.

We have a little of our second period of fifteen minutes remaining, and I am going to ask Dr. Shlevin if he has any comments.

DR. SHLEVIN: No.

MODERATOR PALMER: I will go back to Dr. White.

DR. WHITE: I couldn't agree more with Dr. Given.

MODERATOR PALMER: This is wonderful. We are all agreed. Then we will proceed to the second hypothetical patient.

Hypothetical Patient No. 2:

Pregnant diabetic, age twenty-six years. Duration of diabetes, fifteen years. Primipara, grade II retinopathy, urine albumin one on basis of three. Blood pressure 150/100. Course average to thirty-second week on low salt diet, no gross edema, wt. gain—12 lbs. During next two weeks, urine albumin increased to two, blood pressure 165/100, wt. increased 8 lbs., pitting edema, hydramnios, Grade II.

Dr. Shlevin, I have asked you to open the discussion on this patient.

DR. SHLEVIN: In this case, I am less concerned about the management than I am about a few other things. First, I would want to know something about the history of this patient prior to pregnancy. Did she have hypertension? Did she have retinopathy? How severe was the albuminuria, the diabetes and so on? And then, of course, I would want to know something else. I would like to know what hydramnios "grade two" is. I have enough trouble remembering Dr. White's classification and different degrees of retinitis, but I have not come across the term of hydramnios "grade two."

The reason that I say that I am concerned about diagnosis more than about management is that this patient could have intercapillary glomerular sclerosis, possibly the nephrotic stage of glomerular nephritis, but I assume that this is a case of pre-eclampsia. If my assumption is correct, I would immediately hospitalize the patient. That goes without saying. The next thing I would do is that I would get my obstetrician, and after this patient is studied and stabilized, I would advise the interruption of the pregnancy. I don't believe that one can procrastinate in the thirty-fifth week, and you have only two choices. You either have induction from below or a cesarean section. Knowing that in a primipara in the thirty-fifth week the cervix is not going to be ripe, it leaves you with only one method, which would be to do a cesarean section.

Just a word or two about our own experiences with pre-eclampsia. In the era before 1950, we temporized with toxemia cases, and our mortality rate in the fetus was approximately 16.7 per cent. All these deaths took place in utero. Since 1950, employing more aggressive tactics, our mortality rate in the fetus—and we have just lost one—is 6.7 per cent, and the loss in that fetus was not intra-uterine, it was a neonatal death. Thus I think that the era of temporizing is over, and the present needs call for an era of action.

MODERATOR PALMER: Thank you, Dr. Shlevin. As stated in the agenda it is assumed that this patient is being seen for the first time by the physician, the obstetrician and the internist. It is true, in this instance and in many instances, that we would like to know a lot of things about the patients which are not included here, but this is all of the presenting evidence. I assume that there are a good many pregnant women who are seen, strange as this may seem, for the first time by their doctors near the end of the second trimester, or the beginning of the third trimester. I am quite certain that this is so, outside of diabetes centers. Dr. White has been asked to carry on the discussion about this patient.

DR. WHITE: Like Dr. Shlevin, I, too, am not quite sure about the diagnosis, whether this is decompensated nephropathy in pregnancy or superimposed toxemia. I think our major therapeutic problem is the management of hydramnios. We would hospitalize this patient at once, restrict the sodium, use mercurials and various diuretics, and give her about three or four days to see if she would respond to medical management. Our fetal mortality in week thirty-four is high enough so that we would play for time. If the patient did respond, we would try to carry on as long as possible. If the patient did not respond, we would do a transabdominal amniotomy on this patient. The fluid would be removed rapidly in the course of fifteen or twenty minutes. Then if everything went well, we would try to carry her through week thirty-six. If not, she would be delivered at the end of week thirty-five.

As Dr. Shlevin has said, if signs of toxemia increased, even ever so little, we would consider this an indication for an emergency delivery; and if the mother complained of loss of fetal motion at this period, that would be another sign for immediate delivery. Again, we would attempt a pelvic delivery, and then only after that failed do a cesarean section.

MODERATOR PALMER: I am going to ask Dr. Given to discuss this patient.

DR. GIVEN: Dr. White, the honeymoon is over. Speaking as an obstetrician about toxemia, I have to disagree somewhat with what Dr. White said. The incidence of fetal mortality in severe pre-eclampsia in the nondiabetic infant in our institution has been consistently 18 per cent over the last ten years. As Dr. Shlevin says, we had a great tendency in the earlier days to temporize with these patients, and we were fooled by this word "improvement." The treatment of toxemia means the treatment of a disease of unknown etiology. Therefore, the treatment is absolutely nonspecific.

One attempts to dehydrate the patient with mercurials and oral diuretics. One tries to control the blood pressure to prevent eclampsia, yet one must not lower the blood pressure so far that the patient goes into anuria, and that has happened; we use reserpine, which is of very little value, and paraldehyde and other sedatives, but again the treatment is purely empirical in an effort to control the symptoms. We have found out the hard way that just because the blood pressure comes down and the edema goes, the toxemia still persists, and the baby is getting sicker every day. In our most recent study of toxemia, we found that there was a direct correlation between neonatal and intra-uterine death, and the number of days one temporized with the patient. We have now come to the feeling that we

should not even let the patients "cool off" too much, to use the common term, but as soon as we have them reasonably well controlled, the baby should be delivered. To that degree, I disagree that we shouldn't wait on this patient at all. Were we presented with this patient, we would try to deliver her within twenty-four hours. The problem would have been much more interesting if it had existed at thirty-two weeks, and maybe, if we have a minute left, I should like to ask Dr. White what she would do if she was approached with the identical problem at thirty-two weeks, because I do not know what to do.

DR. WHITE: At thirty-two weeks, I would temporize, because our fetal mortality under thirty-three weeks is extraordinarily high.

MODERATOR PALMER: I promised to allow one or two spontaneous questions from the floor, other than our regular question period. Does anyone have a question in connection with this particular case which we are now discussing?

DR. TOLSTOI, (*New York*): How would the fetal heart sounds influence one's mode of action in this particular case?

MODERATOR PALMER: Doctor, there are no other data than those which are presented, and you are seeing the patient for the first time.

DR. TOLSTOI: Let us say the first heart sound was bad.

DR. WHITE: In spite of the fact that the heart sound, the first heart sound, was bad, and this patient complained of loss of motion, and that we were sure, really sure, of the gestational age, we would not deliver this baby. We would be too afraid of the complications associated with prematurity, such as retrolental fibroplasia, and so forth.

DR. HANFORD, (*Atlanta, Georgia*): I wonder how frequently in a primipara at the thirty-fifth or thirty-fourth week of pregnancy, whom we attempt to deliver from below, this procedure will be successful, and how often eventually will a cesarean be done?

DR. GIVEN: I think that, in general, a girl four weeks from term can be induced only with great difficulty. It is perfectly possible to induce any patient, but it may take five or six sessions, first to efface the cervix, and then to dilate it. Certainly a diabetic could not tolerate this. The patient needs a cesarean section to be delivered easily at that point.

DR. SHLEVIN: I cannot quite agree with the situation in the thirty-second week. If there is evidence of progressive toxemia, I believe you have to take the calculated risk. If you are going to go along and temporize, you invariably run into a fetal mortality. In our experience, knowing that we might have complications in the newborn of hyalin membrane disease, with atelectasis, I think that the lesser of two evils is to go in and interrupt that pregnancy. We have had survivals at the thirty-second week.

One of the things I think that perhaps Dr. Given might be called upon to answer is that the terms we are using today on weeks may need some clarification. We say delivering in the thirty-sixth week, the thirty-seventh week. Might it not be better to say that the patient is delivered fourteen to twenty-eight days before the expected delivery? Weeks can get you into trouble. It may be the start of a week, or the end of a week, and that may make a difference one way or the other.

MODERATOR PALMER: Thank you, Dr. Shlevin. Some time still permits for another question or two from the floor, in connection with this particular patient under discussion. If there are no questions, Dr. White had a comment or two to make on the statistical phase of this problem.

DR. WHITE: As Dr. Given has suggested, there are three present modes of handling the obstetrical diabetic patient. One referred to here is nonintervention, defined as carrying the patient to term, unless there is an obstetrical indication, while giving the patient the very best possible diabetic care, and the handling by obstetrical indications. The second mode is early timing of the delivery, and the third, treatment of diabetes, early timing of delivery and the addition of female sex hormonal therapy.

Dr. Given has given statistics today in reference to the first method of handling. The largest series is that gathered by Dr. Oakley, comprising about 450 patients where, "after viability"—and here is a problem of definition—after the twenty-eighth week, the perinatal loss in this group was 45 per cent. This seems to me an implication that in the diabetic woman, functionally, structurally and chemically—her placenta and also her fetus —differ in no way from the normal.

The rationale for the second mode of delivery, its early timing, was directed largely against the classical accidents, the intra-uterine death. This accident can occur at any time, but tends to have its peak in week thirty-six, which has commonly been selected for delivery. In the majority of series of any size where this method of handling has been used, the mortality after viability in week twenty-eight, is plus or minus 30 per cent. In 1936, we became dissatisfied with such results and have added female hormonal therapy. This corrects the imbalance which occurs as most workers now agree,

acts as a lipid clearer, as a vasodilator, and promotes also the growth and development of the endometrium and placenta. In our 802 patients treated in this fashion, the fetal loss is 13 per cent after week twenty-eight, and up to two weeks after delivery.

Good treatment of diabetes is the preventive part of our program; the early timing of the delivery is corrective; but the use of female sex hormonal therapy is protective. Better results will be achieved when better drugs or agents are discovered.

MODERATOR PALMER: Thank you, Dr. White. We will now pass on the fourth and final phase of this panel, and in this case, each of the panelists will be allowed two minutes to speak on most anything he elects. I will now ask Dr. Shlevin to comment on what priority should be given to control of the diabetes as indicated by blood sugar levels among the factors influencing fetal survival.

DR. SHLEVIN: This is a very difficult question to answer. Fetal survival does not depend upon any one segment, but it is apparently due to the understanding, the experience, and the good judgment displayed by the internist, the obstetrician, and the pediatrician. Of course, you must have the cooperation of the patient.

As far as taking the height of blood sugars alone, or with glycosuria, I don't think that we are today in a position to draw any conclusion one way or the other as to whether they will influence fetal survival. It is rather interesting to note that about a year ago Dr. Priscilla White, in one of her publications, compared the blood sugars, or the average blood sugars in those cases where there was fetal survival, with that of fetal death. She showed that in the group of mothers with living babies the average blood sugar was 145 mg. per cent, and that in those where there was fetal death the average was 156 mg. per cent. She did not consider this of any great statistical difference, and looked for causes other than in the level of blood sugars and the urine, in order to explain the success or failure. As far as I am concerned, I believe that in the handling of an obstetrical diabetic patient, the aim should be to keep the carbohydrate metabolism under control, even though we do not always attain Utopia.

MODERATOR PALMER: I believe Dr. Shlevin has answered that question, and it seems to me that his comments indicate that the better we control the diabetes, the better chance we have to obtain a live baby. Dr. Given, would you care now to comment upon this?

DR. GIVEN: I first want to comment on your last statement, Dr. Palmer, and then on some practical points during the delivery by cesarean section of a diabetic mother.

The first point I failed to emphasize is that in all our work, we have controlled our patients by clinical technics. That is, they have had a free diet, exclusive of concentrated sweets, and they generally have had one dose of long-acting insulin daily. We have taken blood sugars every week in the last 113 diabetics. We do not get the blood sugar back until the next week, so this is of no value, since the insulin requirement may double in that time. I do not have time to show the slide of the blood sugars, but I am sure that even those who feel strongly about chemical control would agree that our control has been good. I think far too often people have considered clinical control to mean lack of control. It *means* control.

Now that I have taken care of that problem, I will go on to some practical points about the control of the diabetes during delivery. If the patient is in labor, she should not be given analgesic drugs under any circumstances. The only thing we give our patients is atropine. This is because demerol or morphine have a depressing effect on the baby. A catheter is kept in place, and the urine is studied every hour. The patient is given an infusion of glucose and water, covered with insulin, and continued throughout her labor or throughout the cesarean section. At the time of delivery, or at the time of section, no general anesthesia is used until the baby is delivered, or until it is almost deliverable. In the case of a section, we use straight local anesthesia down to the uterus, then put the patient to sleep, and the baby is removed instantly. We do not use spinal anesthesia because the occasional drop in blood pressure has been found to depress the baby.

The third principle of importance is that, before any effort at resuscitation is made with these babies, the airway must be thoroughly suctioned out and cleared, and the stomach must be empty, because of the baby's tendency to regurgitate and to aspirate. The fourth principle is minimum handling. Nothing is more harmful for the baby of a diabetic mother than an eager intern. I think one of the chief values of incubation is that they cannot be handled too much. The babies are all dehydrated and not given glucose. It has been shown to be unnecessary. But the most important part of the neonatal care is constant observation, and certainly special nursing is absolutely essential. The pulse rate and respiratory rate are taken every fifteen minutes, and any evidence of passive congestion and early heart failure is noted. If such appears, we digitalize the baby. The babies get oxygen therapy, antibiotic therapy, and if they survive forty-eight hours, we have generally found that they will survive.

MODERATOR PALMER: Thank you, Dr. Given.

DR. WHITE: May I disagree with Dr. Given on one point? It is possible for patients to walk out of the office the same day with a slip in their hand giving them their blood sugars and change in treatment.

DR. GIVEN: I think I can answer that. We carefully do not look at ours until the next week, because we know they are of no value.

MODERATOR PALMER: Now we are getting down to the fun part of this panel, as you can see. Dr. Wilkerson did not choose anything to talk about in the last quarter, but he might like to make a one-minute comment or statement on the significance and any suggested follow-up of overweight babies, child and mother, among non-diabetic pregnant women.

DR. WILKERSON: I have no figures to quote, but I should like to make three or four statements, and I will stick my neck out when I make them. I think that the urine of pregnant mothers should be tested for sugar, but done with the oxidase method, not with other methods, since most of them give you total reducing substances. We have some evidence to indicate that this is significant. Secondly, I think that big babies definitely presage or indicate a prediabetic state. I think our work has already shown that this may be corrected. My personal opinion, based upon observation only and certainly not an official opinion, is that more diabetes is developing in those cases that were not corrected with insulin as compared with the cases in which insulin was used. I emphasize that only through study and observation of cases over a long period of time can we obtain data about the actual effect upon the occurrence of frank diabetes.

We have been disapointed to find in the work of Dr. Keith Vance and Dr. Brian Little, which will appear soon in the *Journal of Obstetrics and Gynecology,* that in a study of some 200 of our cases, there appeared to be no evidence that 17-hydroxycorticosteroids are increased, or are any different in the various groups that I have presented to you.

MODERATOR PALMER: Thank you, Dr. Wilkerson. We have now come to the question and answer period, and we have many interesting questions. The first question which Dr. White will answer is: What method do you use to induce labor in diabetic patients at thirty-four to thirty-six weeks?

DR. WHITE: We use pitocin drips for induction, if the cervix is not favorable.

MODERATOR PALMER: Thank you, Dr. White. The second question is also for Dr. White: What are indications for the cesarean section versus induction of labor?

DR. WHITE: Breech presentation is still an indication in our group of patients, and of course a past section and failure of progression of labor after about an eight-hour trial.

DR. GIVEN: May I add an important point there? I think another indication for cesarean section is the presence of an excessive-sized baby. The infant mortality on delivering babies over 5,000 gm. from below is close to 50 per cent, and there is a tendency to underestimate the size of a baby in a pregnant diabetic mother. I have a rule of estimating as high as I possibly can go in my own mind, and then adding 500 gm. If the baby weighs over 4,500 gm., the chances of severe shoulder distortion are so great that one should prefer a cesarean section from the obstetric point of view.

DR. WHITE: May I add that with the management outlined, we do not have these excessive-sized babies.

MODERATOR PALMER: A third question: How valuable is it to perform glucose tolerance tests during each trimester of pregnancy in patients either with a previous history of having had large babies, or who have been themselves large babies at birth. Dr. Shlevin, would you answer that please?

DR. SHLEVIN: I think postprandial blood sugars, urines and glucose tolerance tests should give the diagnosis in most cases. However, in the light of newer work with steroid hormones, it has been shown that the glucocorticoids increase as pregnancy goes on, until a few days after delivery. You may, during the first trimester, find a normal tolerance curve, maybe an equivocal one during the second trimester, and you may not catch up with it until the final trimester of pregnancy. So that, if you are going to do any detection or searching for diabetes, you must probe; you cannot stop.

DR. WILKERSON: Dr. Palmer, I agree with Dr. Shlevin completely, but if I may, I think I can add a little more information about this question. It was shown on the screen, but not commented upon, that in 134 women who had a negative glucose tolerance test in the first trimester and received another tolerance test in the second trimester, two were positive in the second trimester, or 1.5 per cent. In 1,253 women who had a negative glucose tolerance test in the second trimester, and whose test was repeated in the third trimester, ninety-eight were positive in the third trimester, or nearly 10 per cent.

MODERATOR PALMER: Thank you, doctor. Apparently, continued stress does collect its toll. Dr. Wilkerson, you have been asked to clarify this point. Please comment further on the diagnosis of reducing substances in the urine of pregnant women. Does 68 per cent positive mean 68 per cent of all pregnant women?

DR. WILKERSON: In trying to speed when I first talked, I failed to make it clear that I was describing

two different groups which actually may not be comparable. One hour after 50 gm. of glucose in lemon juice, regardless of prior food intake, there were 68 per cent of *all* pregnant women who had one plus or greater positive results for urine sugar with Benedict's method. In the beginning of our study we did urinalyses on nearly 1,000 women with Benedict's test, and gave up the idea of using glycosuria as an indication for doing glucose tolerance tests. Remember, however, that we were doing blood sugar tests also, and we probably would not have given up the study of sugar in the urine if we had not also been doing blood sugars. Recently we have attempted to do a little work on the comparison of urinalyses with oxidase tests, Benedict's tests and paper chromatography. With only a few specimens tested, and these in only a preliminary way, there appears very little difference between paper chromatographic results and oxidase results. I cannot offer an opinion as yet. We hope to do a study of this question at a later date.

MODERATOR PALMER: Thank you, doctor. A question for Dr. Shlevin. Is there any evidence that mercurials are harmful in the presence of diabetic nephropathy?

DR. SHLEVIN: We have used ammonium chloride, Diamox and mercurials, and have found no trouble as result of using any of them, so that we do not hesitate if we feel that they are indicated.

MODERATOR PALMER: What happens to the mother's insulin requirement, if the fetus dies in utero during the last trimester?

DR. WHITE: I think this an excellent question. We look upon a sudden improvement in diabetes as indication of the possibility of impending uterine death, and consider it a bad sign, not a good sign.

MODERATOR PALMER: Thank you, doctor. Is the incidence of pulmonary complications in the neonatal period greater after cesarean section, or after delivery from below?

DR. GIVEN: Contrary to common opinion, it is not any higher.

MODERATOR PALMER: Given a markedly obese diabetic, 250 lbs., with well-controlled diabetes, but mild acidosis, presumably due to marked caloric restriction: Is acidosis of this type harmful to the fetus?

DR. WHITE: In a diabetic, I think it could precipitate keto-acidosis, and therefore would be.

MODERATOR PALMER: Is there an increase in the ABO hemolytic disease in insulin-treated diabetic pregnancy, since it has been shown that commercial insulin preparations contain blood group antigens? Who wants to answer that?

DR. WHITE: I think the answer is no.

MODERATOR PALMER: In view of the findings in England in a carefully controlled series, that the use of estrogen by mouth did not result in any improvement in fetal salvage, does Dr. Given intend to set up a controlled study, or will every patient be given hormone therapy?

DR. GIVEN: I should like to talk a little about that English study which was certainly disappointing. First, this study was conducted by two groups of workers in two hospitals. That is bad to begin with. Secondly, the patients were given oral stilbestrol, which Dr. White has never advocated; and thirdly, the series was terribly small, only seventy-six patients, as I remember, with controls. I think their study can be discounted as not proving anything, particularly at the moment. In doing a controlled study, obviously it would be valuable to give alternate patients hormone therapy. If one considers that the average clinic sees so few pregnant diabetics, it would take a cooperating group of clinics to do a good study, and that again adds many problems. But it would be preferable to give alternate patients hormone therapy, until one has a series of several thousand patients.

MODERATOR PALMER: For Dr. White: If hormones as they are using them today parenterally, were started near the end of the first trimester, what would be the approximate retail cost in American dollars to the patient by the time the patient is delivered?

DR. WHITE: We were using a preparation which added about $100 to the cost of obstetrical care. Right now, we are using an expensive preparation which is costing the patient nothing, thanks to E. R. Squibb & Sons.

MODERATOR PALMER: Dr. Given, are all the expensive hormones recommended really justified in an eighteen-year-old diabetic primipara?

DR. GIVEN: I think Dr. White ought to answer that question. We have used no hormones to date.

DR. WHITE: It seems to me that an eighteen-year-old is a very serious problem, because even in the general population, she would be a candidate for toxemia, and should be given, therefore, what anyone considers as the best form of treatment; so in my hands, I would feel it justified.

MODERATOR PALMER: Dr. Shlevin. Is there any evidence that there is a lowered renal threshold for ketone bodies as it happens so often for glucose during pregnancy? This is obviously important in the assessment of the seriousness of the ketonuria in diabetic pregnancy.

DR. SHLEVIN: I cannot answer that with any finality. We have been cognizant of ketone bodies in the urine in some normal nondiabetic pregnancies without any adequate explanation. We have also been able to pick up

a few cases where ketones appeared in the urine before there was any other laboratory evidence of diabetes. I think that is a good question, but I think it is going to take a little more time and experimentation before we can give the answer.

MODERATOR PALMER: In other words, you do not know. You feel we do not know whether the threshold for the ketones is lowered, as the threshold for glucose so frequently is. Here is a good question. Dr. White, in what percentage of cases have you noted calcification of the distal femoral epiphysis as a guide to maturity of the fetus?

DR. WHITE: I do not know whether we are polar radiologists in Boston, but we have not found this to be a helpful guide in determining the age of the patient.

DR. GIVEN: I agree with that completely.

MODERATOR PALMER: What does Dr. White think of the Smith treatment with only estrogens, as opposed to the combined progesterone and esterone treatment?

DR. WHITE: George and Olive Smith, dealing with what we would consider the less severe obstetrical problem, in our classes B and C, had good results with oral therapy, but recently, for the severer classifications, they have added parenteral therapy in the form of progesterone, or very large doses of progesterone given in the various ways popular at the moment.

MODERATOR PALMER: Dr. Given, why submit patients to induction of labor or vaginal delivery when section can be done with less trauma to both mother and baby?

DR. GIVEN: Cesarean section is simply a method of delivery, and all statistics will show that the mortality rate is just as great after cesarean section as it is after easy vaginal delivery. I don't mean a high forceps after thirty-five hours of labor to be an easy delivery. But if a patient is two or three centimeters dilated and has a soft cervix, simply rupturing the membranes will precipitate labor, and one can count on four to six hours of easy labor. Those babies do just as well as the section babies.

MODERATOR PALMER: If maternal vascular disease and fetal loss are not considered to be contraindications to pregnancy, what about the eugenic aspects? That is the increased incidence of diabetes in the offspring. Is this not a contraindication?

DR. WHITE: That is, of course, very serious, and a very important question. The chances of the offspring of a single diabetic parent eventually developing diabetes are actually 22 per cent for their entire life span. But since one out of every three of us is also an hereditary carrier of the disease, I do not think we could carry genetic teaching too far.

MODERATOR PALMER: May I comment on that? If our efforts to prevent the joining of diabetic family trees has not been successful, I think, that once pregnancy has occurred, this in itself is no indication for abortion.

Dr. Wilkerson, are your figures for abnormal glucose tolerance somewhat lower than those usually expressed?

DR. WILKERSON: From a perusal of the literature on the subject, we expected 8 to 10 per cent of pregnant women, previously not suspected of any abnormality of carbohydrate metabolism, to have an abnormal glucose tolerance test curve at some time during their period of gestation. Our figures so far are only about half of what we expected to find.

MODERATOR PALMER: We have just about completed these questions. I would like to express my appreciation and that of the panel for your patience and particularly for your interest.

EDITORIALS

WHAT THE PATIENT SHOULD BE TOLD ABOUT THE ORAL HYPOGLYCEMIC COMPOUNDS

Every diabetic patient inquires hopefully about the possibilities of oral therapy. Good prospects for successful control of blood sugar can be held out to those whose diabetes developed after they were forty years of age, but for the patient who acquired detectable diabetes in childhood there is, with very rare exceptions, no prospect of benefit from tolbutamide.* Disappointing prospects may be less poignant if it is shown that because of tolbutamide and related substances, research in diabetes has reached an intensity never equalled in the past. Also, there is some comfort in knowing that preliminary reports on newer orally effective products indicate a favorable influence on hyperglycemia and glycosuria in some young patients. The truth about the inffectiveness of the sulfonylurea compounds is accepted with better grace if hope is not extinguished. These patients may not feel so disappointed when they learn that the oral preparations are a matter of convenience only and that they have no other known advantages, but rather several disadvantages over insulin therapy; that insulin after all is still the ideal agent as it corrects, physiologically, what they lack; that oral therapy holds no prospect whatever for a cure of the diabetes and does not decrease the need for attention to their diets nor to the testing for glycosuria; that insulin therapy must be resumed during acute complications, a procedure which may be more complicated than if one merely had to adjust one's dosage of insulin; and that if physicians specializing in the treatment of diabetic patients had a choice of only one drug, insulin or an oral preparation, the choice, because of the need for insulin when complications threaten life, would always be insulin.

For the "adult acquired" diabetes and especially in those patients over forty years of age, the physician's approach may be quite different from that outlined above. Instead of engendering undue optimism in these patients, the majority of whom will respond favorably to oral therapy, an attitude of caution is to be recommended. A "wait and see — and hope" attitude prepares patients for the disappointment should they, for one reason or another, be obliged to return to insulin therapy. The idea of a cure has been planted, without the slightest foundation, in the patient's mind by some articles in the press. This should be dispelled.

The patient is made aware that we are traveling an uncharted course and must be more alert than ever until the potentials, good or bad, of these drugs, as they affect the great variety of patients under a great variety of circumstances, are familiar to us.

Diabetics are usually better trained than other patients and they accept readily the need for daily communication with their physician for the first week or two of oral therapy if appreciable reductions in insulin, or its omission, have been adopted at the onset of oral therapy. They are instructed to test every specimen of urine, immediately after voiding, for sugar and acetone for at least four days after insulin has been greatly reduced or omitted. Persistent glycosuria means that the oral therapy will be inadequate, but the prompt appearance of acetone is a danger signal and demands the immediate return to insulin treatment. The occurrence of increasing ketonuria in the absence of an acute complication is, I believe, an indication that the individual is not a candidate for oral therapy.

Individualized instruction regarding unfavorable effects of oral therapy appears advisable. Side effects need not be elaborated upon if the patient is cooperative and can be relied upon to remain under close supervision and to report unusual symptoms. For the less reliable patient, some of the possible side effects, even though rare, are brought to his attention. This encourages cooperation in this early phase of a new treatment. It is well that all patients taking tolbutamide, or related agents, should know that they, as well as the doctor, are on a long-term pioneering project in therapy. The outlook is favorable but until the mode of action of these drugs is clearly understood, their long-term use is not devoid of apprehension nor should it be without caution.

Approximately 80 per cent of adult diabetics are overweight when they seek treatment. Two thirds, at least, of this large group are candidates for oral therapy and spectacular control of the glycosuria and hyperglycemia with tolbutamide may be expected. But, it is well to sensitize these patients to the fact that no oral therapy

* Available commercially as Orinase (Upjohn).

is a suitable substitute for an appropriate reduction in weight; that tolbutamide does not increase appetite, hence supplements well the benefits of a reducing regimen for the overweight patient; and that the need for drug therapy decreases and may disappear as the weight approaches the ideal. Knowingly to accept the advantages of tolbutamide and to ignore those of a temporarily reduced diet may be likened to the behavior of children who accept privileges but shun responsibilities.

The instruction of patients regarding oral therapy is for the most part an individualized affair but it is pertinent that all know some salient facts about tolbutamide:

a. It is effective in controlling the diabetes in the majority of the older and is rarely effective in young diabetics or in those who acquired diabetes while they were young.

b. It is not a form of insulin nor does it act like insulin.

c. It is not a cure for diabetes.

d. When the diabetes may be controlled by diet alone, the drug is unnecessary.

e. It is ineffective during acute complications, notably acute infections, surgical procedures and ketosis.

f. Its favorable effect is transitory (four to six months) in some patients.

g. It does not reduce the need for attention to *diet, tests for sugar and acetone* in the urine. These measures are of special importance in the first few days of oral therapy.

h. There are no advantages except in rare instances in using insulin and tolbutamide simultaneously.

i. Unlike the great variety of doses of insulin, the dosage of tolbutamide is relatively uniform, preferably at 1.0 or 1.5 gm. and not more than 2 gm. daily given in divided doses for long-term treatment.

j. The dosage of tolbutamide is changed only under the physician's direction. Excessive amounts have been known to increase the level of the blood sugar, the degree of glycosuria and the incidence of unfavorable side effects.

k. The change from insulin to oral therapy is accomplished by different plans according to the severity of the diabetes and the likelihood of a favorable response. For some, indeed for the majority, this can be accomplished on an outpatient basis. For others, hospitalization is highly desirable.

l. Hypoglycemic reactions are most likely to occur during the transition period from insulin to tolbutamide. Such reactions are rare with tolbutamide alone but when they do occur, the symptoms are identical to those of a hypoglycemia due to insulin. The treatment in both cases is the same.

m. Studies, in addition to blood sugar determinations and urinalyses, should be done at frequent intervals until it is certain that the new drug is well tolerated by the patient. These studies will include especially blood counts and the checking of the function of the liver.

n. Research workers and physicians have zealously guarded the welfare of diabetic patients in the development of oral therapy and this keen acceptance of responsibility has been shared by the pharmaceutical firms interested in these new agents.

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OCULAR NERVE PALSY IN DIABETES

Attention has been called recently to the frequency of ocular nerve palsy associated with severe headache occurring in diabetic patients.[1, 2] This syndrome of ocular nerve palsy associated with headache has been recognized for a long time. It is a rather frequent disorder, particularly when the paralysis is that of the oculomotor nerve. It usually comes on suddenly and is accompanied by severe pain on the same side of the head. Most of the patients who show this disease also demonstrate hemorrhages and exudates in the fundus as well as evidences of vascular disease in the retinal vessels.

Dieulafoy[3] in 1905 collected several cases of extraocular muscle paralysis due to diabetes mellitus. The association of such paralyses with diabetes mellitus has been noted in large series of patients by several investigators.[4, 5, 6, 7] Recovery is the rule in these cases. Waind[2] has noted that this is one of the most important features of this syndrome.

Speculation has been made concerning the etiology and exact nature of the lesion. It is suggested that it is of vascular origin, perhaps a minute hemorrhage either into the nerve trunk or about the nucleus of the oculomotor nerve. This theory is supported by the rapidity of onset in a great majority of cases with complete paralysis of the nerves involved. The tendency toward total regression has been mentioned, although recovery of function may require several months. Vitamin deficiencies frequently noted in diabetes mellitus and polyneuritis have also been suggested as causes of the ocular palsies.[6, 8] A recent pathohistologic observation has been made in diabetic oculomotor palsy by

Adams, Hakin, and Dreyfuss. They noted a gross swelling of the intraorbital portion of the third nerve with extensive destruction of medullated fibers in its central portion.

Controversy exists as to the frequency with which nerves to extraocular muscles are affected; according to Waite and Beetham[4] and Walsh,[8] the sixth cranial nerve is the most commonly involved. Other authors[9] have recorded predominance of third nerve paralysis. The fourth nerve may be affected occasionally.

There are many causes of third nerve involvement from which the syndrome must be differentiated. Lesions of the third nerve fibers within the central nervous system are usually accompanied by other neurological signs and symptoms. Benedict's syndrome is characterized, for example, by homolateral oculomotor paralysis with contralateral intention tremor. When the cerebral peduncle is involved along with the third nerve, Weber's syndrome is diagnosed by the presence of oculomotor paralysis on one side and hemiplegia on the other. When the third nerve is involved in the cavernous sinus and the supraorbital fissure, it is practically always accompanied by involvement of other oculomotor nerves as well. Various inflammatory conditions such as syphilitic and tuberculous meningitis may produce third nerve paralysis. The inflammatory process of these diseases usually catches the third nerve as it emerges from the central nervous system around the chiasm, pons, and temporal lobes. Whenever meningitis of this sort is responsible, the lesion is usually bilateral. Purulent meningitis, on the other hand, usually involves the sixth nerve and not the third. A variety of toxins such as alcohol, lead, arsenic, and carbon monoxide have been said to produce a polyneuritis and produce a similar change as that seen in diabetes mellitus.

A rupture of an aneurysm at the base of the brain may catch the third nerve and produce a characteristic picture. Most of these aneurysms are situated at the branching of the internal carotid. In this site the nerve is especially vulnerable. Usually the individual has severe pain on the side of the face on which the third nerve is paralyzed as well as severe headache.

Migraine has been said to produce recurrent third nerve paralyses. Tumors which involve the third nerve usually impair the function of other oculomotor nerves, along with the third nerve, and often involve the trigeminal nerve.

An awareness of this syndrome and the exclusion of the other possible etiologies in a patient with diabetes mellitus allow one to give a more favorable prognosis. The exact frequency of this complication has not been well established, and further work is required to establish the exact pathogenesis of these palsies.

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Communication in Medicine

The trials of history taking are only slightly more taxing than the trials of history reading. Forgetting the communicative obstacles that he has had to overcome in getting the patient's story, the student artfully, perhaps vengefully, invents some of his own in setting it down. This is supposed to keep the attending physician on his toes. The patient, reads the professor, gives an Hx (history) of certain Sx (symptoms), consisting mainly of SOB (shortness of breath) and PND (paroxysmal nocturnal dyspnea) which failed to respond to NG (nitroglycerine) under the tongue. The social Hx reveals a lack of TLC (tender loving care) in childhood. After a thorough Px (physical examination), and with the help of a BUN, PSP, EKG, and EEG, the case is Dx'd (diagnosed) and finally Rx'd (treated). I leave you to guess who is Vx'd (irritated).

By Henry T. Ricketts, M.D.,
From *The Journal of the Bowman Gray School of Medicine*, Vol. XV, No. 3, June 1957.

OLE CHRISTIAN ZIMMERMANN, M.D.

Johann Conrad Brunner
1653-1723

Ole Christian Zimmermann, M.D., Thun, Switzerland

Johann Conrad Brunner, known to every medical student for his description of the duodenal glands, should be appreciated also for his enquiring research into the role of the pancreas. While a practising physician in Diessenhofen, a small town at the northern border of Switzerland, he observed the effects of excision of the pancreas to settle the question whether this organ was essential for life.

He reported his experiences in two publications. In the first, *"Experimenta nova circa Pancreas, accedit Diatribe de Lympha et genuino Pancreatis usu,"* Amstelaedami 1683, he noted in the sixth experiment, performed on July 19, 1679 (?) that frequent urination, immoderate drinking and a voracious appetite followed the extirpation. Also in the seventh experiment, dated March 23, 1683, Brunner comments on the intensive thirst of the animal.

In the second report, *"De Experimentis circa Pancreas novis confirmatis. Miscellanea curiosa sive Ephemeridum Medico"* — Physicarum Germanicarum Acad. Imp. Leopold, Natur. Curios. Dec. II Annus VII 1688, Norimbergae 1689, he described in full detail, accompanied by an excellent drawing, the technic of a pancreatectomy performed on a neighbor's hunting dog on Oct. 6, 1685. On the following day abundant urination was noted, on October 9 increasing appetite, but on October 12 the dog escaped and returned to his own master who refused to return him to the experimenting physician. For a long time Brunner tried in vain to get hold of the dog, and six months passed before he caught the animal again. A post-mortem examination showed the pancreatectomy to be incomplete.

The repeated observations of polyuria, polydipsia and polyphagia indicated that Johann Conrad Brunner had performed the first recorded subtotal pancreatectomy leading to a Sandmeyer-type of diabetes. Brunner, however, who later in 1686 became professor of anatomy and physiology at the University of Heidelberg, did not connect the symptoms with diabetes. More than 200 years later, von Mering and Minkowski also excised the pancreas of a dog in order to investigate pancreatic function. Again they met the same cardinal symptoms which were similar to those Minkowski had seen in diabetic patients. The fame of Johann Conrad Brunner rests not on his work on the pancreas, but on his description of the duodenal glands which bear his name.

REFERENCE

Ole Christian Zimmermann: Die erste Beschreibung von Symptomen des experimentellen Pankreas-Diabetes durch den Schweizer Johann Conrad Brunner (1653-1723), Gesnerus 2: 109-30, 1945.

BOOK REVIEWS

REDUCE AND STAY REDUCED. *By Norman Jolliffe, M.D. $3.50, pp. 264, Simon and Schuster, Inc., New York, 1957.*

This book, written primarily for the reducer, has gone through seven reprintings of its first edition in 1952. The present second edition has been modified to incorporate recent concepts for the prevention of atherosclerosis so that the diets contain less than 30 per cent of the calories from fat. In addition, low sodium and emergency liquid diets, and simplified diagrams have been added.

The first part of the volume concerns itself with the "Appestat" concept of the appetite and hunger regulating mechanism, tests for obesity, indications for reducing and not reducing, and the basic physiology and mathematics of weight regulation and control. Since this volume is not intended as a thesis on hunger regulation, it would be inappropriate to review it as such. The "Appestat" theory is certainly an oversimplification of the present knowledge of the short and long term regulatory factors of food intake, satiety, and weight. The phrase is, nevertheless, attractive and has become established in both scientific and popular literature. In this work it has been used deftly by its originator to supply a logical concept to the reducer so that he may obtain a better understanding of his problem. The second part

contains the methodology: Diet selection, food values, menus, cookery and an extensive list of calorie counts. Separate small chapters are devoted to "heart saver" (low fat) and low sodium diets with numerous wise hints to make these often burdensome diets more tolerable.

The reviewer is impressed with the merit of this work. It is sound, scientifically accurate and factual. It offers no panaceas or fads but places reducing in its proper place as a prophylactic and therapeutic procedure. It does not appeal to the emotions but to reason, offering the reader a sound and intelligent fund of information which he may grasp easily and utilize sensibly. It may be studied with great benefit by the medical reader as well, certainly, by those interested in diabetes. Nothing like it is available to the serious reducer, and the physician can recommend it to him with all confidence.

CLINICAL PHYSIOLOGY. *Edited by Arthur Grollman, M.D. $12.50, pp. 854, McGraw-Hill Book Co., Inc., New York, 1956.*

This book attempts to present the "basic physiologic principles of clinical medicine" without including general subjects of physiology or clinical medicine, available in current texts. The aim involves considerable selection of material, which is evidenced in the chapters by the twenty-six distinguished contributors. However, even the subject matter included requires compression in order to be treated within reasonable limits, a fact which has left the quality of a synopsis in significant segments of the book. In other chapters, a restricted area has been treated intensively with no attempt at complete coverage of the subject. Opinions may differ regarding the need and desirability of this varied approach, but it does provide an uneven character to the book as a whole. This is not intended as a criticism of the material, since all the chapters are written with authority and at a generally advanced level. An outstanding feature is the timely and valuable analysis of pulmonary function by Drs. Dickinson W. Richards and Andre Cournand. The factors which operate to produce impairment of pulmonary function are categorized, and provide a framework for proper evaluation of the patient with pulmonary disability. The erudition and perspective for which he is remembered are demonstrated in the discussions of carbohydrates, lipid, and protein metabolism by the late Dr. John P. Peters. These sections will prove worthwhile to the individual who desires to refresh his knowledge of the basic principles of metabolism.

The book is recommended reading for all physicians who regard continuing education in principles of human physiology as an important aspect of clinical instruction.

ACTUAL PROBLEMS IN DIABETES, *A symposium. Edited by Prof. Dr. E. Bertram and Dr. J. Kuntze. $1.35, pp. 80, Georg Thieme, Stuttgart, 1957.*

This most valuable transcript of a Symposium on Problems of Diabetes, held in Hamburg in January 1957, contains contributions and discussions from a great number of authorities from Germany, Austria, Switzerland and Sweden.

Since the hypoglycemic sulfonylureas have been in use in Germany for a longer period of time than in the U.S.A., and since carbutamide as well as tolbutamide are employed, the experiences and problems discussed are of great interest. Both drugs appear to have continued to give generally satisfactory results in the management of the stable, maturity onset diabetes. Most speakers agreed that about 28 to 40 units of insulin per day are the upper limits which can be replaced by the oral drug. The importance of adherence to dietary restrictions was stressed. The hypoglycemic activity of carbutamide was found to be somewhat greater than that of tolbutamide in equal doses, but the toxicity of tolbutamide to be less. Some authors recommend use of the latter only, as in the U.S.A., but others would not like to miss carbutamide. The main discussion centered around the two problems of (1) mechanism of action, and (2) drug escape. The concept of α-cell or glucagon inhibition seems to be largely abandoned. β-cell stimulation with stimulation of insulin secretion is now generally accepted as the main or one of the main actions (v. Holt, Kracht, Baender), but no reference is made to Loubatières who first suggested it. The possibility of hepatic action and inhibition of glycogenolysis was discussed by Beringer. Heinsen reported that, in a number of patients, the oral drug lost its effect after an initial period of good control. He called this a tachyphylaxis-like reaction. Various speakers (Constam, Zurich; Brechmann, Hamburg; Stratmann, Stuttgart; Otto, Hamburg; and Pfeiffer, Frankfurt) confirmed this observation of drug escape. In some instances this was thought to be caused by overeating; in others, however, the question was raised of islet-cell exhaustion. Mylius, Hamburg, reported on fresh punctate hemorrhages in the fundi of patients under sulfonylurea treatment, but other clinicians did not corroborate his findings.

ABSTRACTS

Annotation: GLUCOSE-TOLERANCE TESTS. Lancet 2: 33, July 6, 1957.

The author points out the types of glucose tolerance tests presently employed, their advantages and their pitfalls. The conclusion is reached that the intravenous glucose tolerance test is probably the most reliable, despite the fact that more frequent blood samples are necessary.

Annotation: THE ENZYME DEFECT IN GALACTOSAEMIA. Lancet 1:1080, May 25, 1957.

The genetically determined inborn error of metabolism known as galactosemia is discussed. Knowledge of the defect involved, and questions yet to be answered in this condition are brought up.

Annotation: TUBERCULOSIS AND DIABETES. Lancet 2: 131-32, July 20, 1957.

The author comments on the incidence of tuberculosis in diabetics and the course of infection, once it has developed.

Barta, L. (Budapest Univ. Med. Sch., Budapest, Hungary): CARBUTAMIDE IN JUVENILE DIABETES. Lancet 1:1090, May 25, 1957.

The author reports his experience with carbutamide therapy in sixteen juvenile diabetics between the ages of six and thirteen. The blood sugar level, studied in the diabetic children, was not reduced by carbutamide, even in full adult doses, and a combination of carbutamide and insulin did not give good results.

Barta, L.; and Simon, G. (First Dept. Pediatrics, Univ. Med. Sch., Budapest, Hungary): EFFECTS OF CARBUTAMIDE ON CARBOHYDRATE METABOLISM IN DIABETES (Letter to Editor). Lancet 1:1249-50, June 15, 1957.

The authors have studied in the rabbit the effect of carbutamide, with or without cortisone, and the rise of blood sugar following the fall induced by 10 units of insulin given intravenously. With insulin by itself, such a high dose ensures a significant rise of the blood sugar —i.e., outflow of glucose from the liver. If carbutamide is really capable of decreasing the outflow of glucose from the liver, the posthypoglycemic blood sugar rise must also be decreased. In the rabbits used in these experiments this was found not to be the case, and was interpreted by the authors to mean that in spite of carbutamide treatment there was a significant outflow of glucose from the liver.

Bohan, Edward M.; Serino, Girard S.; and Olivere, Peter J. (St. Francis Hospital, Wilmington, Del.): DIABETES MELLITUS, PSEUDOPANCREATIC CYST, AND LOW SALT SYNDROME: PART II. Delaware M. J. 29:123-25, May 1957.

A patient with diabetes mellitus and a huge pseudopancreatic cyst recovered from surgical procedure at which external drainage was performed. The drainage continued for eight months and then ceased.

British Diabetic Association, Banting Memorial Meeting. Lancet 2:124-25, July 20, 1957.

The program of the eleventh Banting Memorial meeting of the British Diabetic Association held in Oxford on July 12 and 13, 1957, is discussed.

Brock, Benjamin L. (Central Florida Tuberculosis Hosp., Orlando, Fla.): THE DIABETIC PATIENT WITH TUBERCULOSIS. Lancet 77:238-42, July 1957.

The coexistence of diabetes mellitus and tuberculosis has long been recognized as a serious public health problem. Pulmonary tuberculosis occurs two to four times more frequently among diabetics than in the rest of the population. Tuberculous infection, almost universal a few decades ago, now occurs in about 50 per cent of the population of this country, whereas tuberculous disease is found in less than 0.5 per cent.

The susceptibility to tuberculous infection is fairly general and is primarily dependent upon contact with the tubercle bacillus, whereas the development of tuberculous disease is individual and dependent on various factors which may be included under the one term, resistance. In addition to other possible causative factors, a newly recognized factor is that of stress.

King has mentioned five conditions to have a direct bearing on the development of tuberculous disease: starvation, gastric resection, puberty, diabetes, and the administration of cortisone. In these conditions, stress, certainly, is a common factor.

The successful treatment of the tuberculous diabetic patient depends upon control of the diabetes and control of the tuberculosis by hospitalization and coverage with modern antituberculosis drugs until the disease has been arrested. It is relatively simple to obtain good regulation in most diabetic patients, provided they cooperate. However, control is often impossible to obtain with any regimen until a patient under emotional stress, with swings from hyperglycemia to hypoglycemia, has had proper psychologic care.

At the moment, the conservative view of rather strict aglycosuria and normoglycemia appears to prevail as far as the tuberculous diabetic patient is concerned. However, a diet that is adjustable to meet the variables in the patient's everyday life is of basic importance, and the correct weight of the patient should be maintained.

It is also most important to set up a schedule for X-raying the chests of known diabetics and examination of the blood of known tuberculous patients. It is agreed that known diabetics should be X-rayed at least every six months.

Burns, Thomas W. (Univ. of Missouri Sch. of Med., Columbia, Mo.): DIABETES MELLITUS: PRACTICAL APPLICATION OF THE LABORATORY. Missouri Med. *54*: 515-18, June 1957.

This paper discusses the practical application of laboratory aids in diabetes mellitus.

Burstein, Robert; Soule, Samuel D.; and Blumenthal, Herman T. (Depts. of Ob.-Gyn., Jewish Hosp. and Washington University Sch. of Medicine, and Dept. of Pathology, Jewish Hosp., St. Louis, Mo.): HISTOGENESIS OF PATHOLOGICAL PROCESSES IN PLACENTAS OF METABOLIC DISEASE IN PREGNANCY. II. THE DIABETIC STATE. Am. J. of Obst. & Gynec., *74*:96-104, July 1957.

This report consists of a study of the histological changes in the placentas of twenty cases of pregnancy in diabetic women. Many of the changes consisted only of an intensification of pathological processes previously described in the placentas of normal pregnant women and of pregnant women with toxemia or hypertension. These include decreased formation of elastic tissue in the umbilical arteries, calcification of chorionic plate and villi, and fibrinoid deposition in villi.

The diabetic group also showed changes in the syncytial buds and increased syncytial bud counts comparable to those found in the hypertensive toxemic group. The significance of these changes, as related to the importance of steroid hormone metabolism in both disease groups, is discussed.

An endarteritis of placental vessels in diabetic mothers has been described which appears not to have been reported heretofore. The resemblance of these lesions to other vascular changes, specifically associated with the diabetic state, has been pointed out, and evidence for such a specificity of this endarteritis has been presented.

Butterfield, W. J. H.; Camp, J. L.; Hardwick, C.; and Holling, H. E. (Med. Research Council, Univ. Virginia Med. Sch., U.S.A. and Guy's Hosp., London): CLINICAL STUDIES OF THE HYPOGLYCAEMIC ACTION OF THE SULPHONYLUREAS. Lancet *1*:753-56, April 13, 1957.

The authors report twenty-nine diabetic patients in whom the effect of seven days' treatment with sulphonylurea (with and without insulin) on various carbohydrate tests, A-V differences in blood α-keto acid levels, peripheral blood flow and the hyperglycemic responses to injected glucagon were tested. In twenty-two patients the fasting blood sugar fell more than 15 per cent. The only significant change after treatment was in the glucose tolerance test, where the blood sugar level fell below the fasting level at sixty and ninety minutes. There was a significant increase in the fore-arm blood flow during treatment. Such changes in peripheral blood flow complicate the interpretation of A-V differences in blood sugar levels. There was a small but significant fall in the fasting level of α-keto acids. The hyperglycemic response to 1 mg. of glucagon injected intravenously was not significantly changed after treatment. The hypoglycemic action of sulphonylureas in diabetics does not appear to be mediated by any of the mechanisms so far suggested by the results of experiments on animals.

Calvert, R. J.; and Caplin, G. (North Middlesex Hosp., London, & Royal Victoria Hosp., Bournemouth, England): THE HOUSSAY SYNDROME. Brit. M. J. *2*:71-74, July 13, 1957.

The authors report a case of Houssay syndrome and also review this subject.

Carrington, Elsie R.; Shuman, Charles R.; and Reardon, Helen S. (Temple University Sch. of Medicine and Hosp.; and St. Christopher's Hosp. for Children, Philadelphia, Pa.): EVALUATION OF THE PREDIABETIC STATE DURING PREGNANCY. Obst. & Gynec. *9*:664-69, June 1957.

A prediabetic state associated with pregnancy was detected in ninety-two instances by means of glucose tolerance tests performed in 621 patients.

The significance of this concept is demonstrated by the differences observed in fetal survival rate. In those patients, diagnosed and treated antepartum, 98.3 per cent survived, while in unrecognized cases the survival rate was only 71.4 per cent.

Earle, A. Scott; Cahill, George F., Jr.; and Hoar, Carl S., Jr. (Harvard Med. Sch., West Roxbury Veterans Administration Hosp., and Peter Bent Brigham Hosp., Boston, Mass.): STUDIES ON THE RELATIONSHIP OF GLUCAGON (HGF) TO BLOOD PEPSINOGEN CONCENTRATIONS. Ann. Surg. *146*:124-30, July 1957.

Glucagon (HGF) administered as a single dose, or as an infusion lasting up to four hours, acts consistently

in dogs to lower blood pepsinogen levels. This action is shown to be unchanged by vagotomy. A similar depression of blood pepsinogen levels is produced by the administration of intravenous glucose. Based on these acute experiments, as well as other available data, it seems unlikely that glucagon acts as a factor in peptic ulcerogenesis.

Flinn, Lewis B. (Med. Dept. and Metabolic Clin., Delaware Hosp.; Memorial Hosp., Wilmington, Del.): FETAL MORTALITY IN PREGNANT DIABETICS. Delaware M. J. 29:174-76, July 1957.

The accumulated evidence to date strongly suggests that, in any medical community, diabetic pregnancies can best be handled by a small group of internists, obstetricians and pediatricians working as a team. Each case must be individualized, but in general, in order to achieve the lowest possible fetal loss, meticulous care of the diabetes is necessary, requiring frequent observation by both the physician and obstetrician, perhaps hospitalization sometime prior to the thirty-eighth week, cesarean section when indicated, and prompt care of the newborn by the pediatrician.

Frank, Ludwig L. (London, England): DIABETES MELLITUS IN THE TEXTS OF OLD HINDU MEDICINE (CHARAKA, SUSRUTA, VAGBHATA). Am. J. Gastroenterol. 27:76-95, January 1957.

The author gives a beautifully detailed history of diabetes mellitus as mentioned and described in the texts of old Hindu medicine. The report is based on translations of three textbooks of Ayur Vedic medicine. In addition, the author gives a short outline of the history of old Indian medicine in general.

Fuller, B. F. (St. Paul, Minn.): THE DIABETIC FOOT. Minnesota Med. 40:233-34, April 1957.

It is necessary to distinguish the "diabetic foot" from simple arteriosclerosis obliterans. Although simple arteriosclerosis obliterans may occur in the diabetic as well as in the nondiabetic patient, it differs from the "diabetic foot" problem mainly in that it is a much more discrete entity clinically, and other factors than ischemia are often of prime importance.

Frequently, one sees extensive ulceration and gangrene of the distal end of the foot with palpable dorsalis pedis or posterior tibial pulses or both present. At an earlier stage of its development one may demonstrate marked pallor of elevation of a toe with absence of pallor of the remainder of the foot and with normal arterial pulsations present. In other words, the arterial insufficiency is usually in the small vessels and frequently is distal to the palpable pulses.

Perhaps the most often overlooked abnormality, and an exceedingly important one, is the presence of anesthesia or hypesthesia of the distal portion of the extremity due to diabetic neuropathy. The initial treatment of the diabetic foot is almost always very conservative. The only exception to this is the presence of an acute, fulminating infection which represents an emergency, rarely encountered since the antibiotics have come into general use.

Gastineau, Clifford F.; Underdahl, Laurentius O.; and Enderlin, Martin (Mayo Clin., Rochester, Minn.): A CLINICAL STUDY OF THE SULFONYLUREAS IN DIABETES. Proc. Staff Meet., Mayo Clin. 32:306-13, June 12, 1957.

Numerous observers have stated that the sulfonylureas are capable of maintaining satisfactory concentrations of blood sugar for a number of months in a generous proportion of patients with mild diabetes. It should be pointed out, however, that many of these patients have diabetes of such mild degree that dieting alone can control the hyperglycemia, and the use of the sulfonylureas does not seem to offer such patients any additional benefits.

The question can be raised whether the mechanism by which sulfonylureas lower the concentration of blood glucose is a desirable one, and whether some complication may not result from long-term treatment. As yet, however, there is no direct evidence to support this speculation.

Another possible question is whether the degenerative complications of diabetes will be seen with more or less frequency after long-term treatment with sulfonylureas. These drugs have not been used long enough to permit evaluation of their effect on the appearance of degenerative complications, but there is no reason to presume that they will be superior to conventional treatment in this respect. In some patients it has proved surprisingly difficult to be certain, even after close observation for several weeks, if the hypoglycemic effect was due to use of these agents and not to changes in diet or other factors. Thus it seems desirable to measure blood sugar levels in a systematic manner before, during, and perhaps after a period of sulfonylurea administration to be certain that the drug is actually exerting a beneficial effect and is not acting merely as a placebo in encouraging adherence to proper diet.

Although serious reactions to tolbutamide are said to be rare, the milder manifestations of its toxicity and the remaining question as to its mode of action warn against long-term administration of the drug except with careful consideration.

Goldsmith, L.; and Moloney, P. J. (Connaught Med. Res. Labs., University of Toronto, Canada): CHROMATOGRAPHY OF GUINEA-PIG NATIVE INSULIN. Biochem. J. 66:432-34, July 1957.

The authors separated guinea pig insulin by reversed-phase chromatography into two fractions, neither of which was neutralized by anti-insulin produced by the guinea pig or by anti-insulin produced in the rabbit, sheep or horse by injection of ox or pig insulin. A mixed solution of ox and guinea pig insulin was separated by chromatography. The hypoglycemic activity of ox, pig, rabbit, sheep and horse insulins was neutralized by anti-insulin produced in the guinea pig, rabbit, sheep and horse by injection of ox or pig insulin.

Gross, John B.; and Comfort, Mandred W. (Sect. of Medicine, Mayo Clin., Rochester, Minn.): HEREDITARY PANCREATITIS. Proc. Staff Meet. Mayo Clin. 32:354-60, July 10, 1957.

The authors describe the pedigrees of two additional, unrelated families in which the hereditary form of chronic relapsing pancreatitis and sequelae have occurred. These additional observations tend to confirm the original impression that in certain families chronic relapsing pancreatitis is transmitted as an autosomal dominant gene.

Haunz, E. A. (Grand Forks Clin., Grand Forks, N. D.): THE INSULIN REACTION. A CRITICAL REVIEW WITH ILLUSTRATIVE CASES. Lancet 77:183-90, June 1957.

It is well known that tremendous amounts of insulin may be given to some patients without ill effect—a phenomenon termed "insulin resistance." On the other hand, a precipitous and persistent decline in the blood sugar level may be seen in so-called insulin-sensitive patients in response to relatively small doses of insulin but still devoid of ill effect or any clinical semblance of an insulin reaction. Another curiosity, less rare, is what might be termed an "insulin paradox." An insulin reaction has been variously reported to occur in the presence of a normal or even elevated blood sugar level. There are many who feel that insulin reactions are based on the rapidity of fall in the blood sugar level rather than on low values per se, although both factors may be operative in many cases.

There is a unanimity of opinion in the concept that hypoglycemic symptoms stem chiefly from an indirect effect on the brain. At this point, opinions are divergent. Some believe that symptoms result from glucopenia of the brain, interfering with multiple cerebral oxidative mechanisms, while others maintain that these symptoms are the specific end result of anoxia induced by cerebral glucopenia. That severe hypoglycemia and, more especially, glucopenia of the brain tissue are capable of producing prolonged or even irreversible and sometimes fatal damage is a fact that should command the respect of every physician. The physician who mistakenly identifies insulin coma as diabetic coma and, hence, injects more insulin cannot justify his error on any basis but incompetence. It is infinitely less hazardous to administer more glucose to a patient in diabetic coma than to give more insulin to a patient in insulin coma!

It is axiomatic that all insulin reactions should not only be treated with glucose as described, but a meal relatively high in protein and fat content should be taken to prevent a recurrence. Moreover, the patient should always consult his physician before taking the next dose of insulin after a reaction. Prophylaxis of insulin reactions should, of course, be the keystone in the arch of treatment. A systematically organized plan of patient analysis, including living habits, diet, selection of appropriate insulin preparations, temperament, and sites and technic of insulin injection, frequently eliminates or reduces the frequency and severity of reactions. When all efforts fail to prevent unpredictable severe nocturnal reactions, an alarm clock awakening the patient at selected intervals during the night may provide the only means of protection, replacing intense fear with some peace of mind.

Heale, T. A. F. (Melbourne, Australia): THE PRESENT-DAY USE OF INSULINS IN THE TREATMENT OF DIABETES MELLITUS. M. J. Australia 1:665-71, May 18, 1957.

A new insulin is a temptation to physician and patient. The physician by favorable reports may be persuaded to change many of his diabetics to the new insulin. The patient may want to use it, believing it to contain some magic not present in his present insulin. A change of insulin should not be made lightly. There are two golden rules: (1) Never change a well-controlled diabetic to a new insulin. (2) Always change a poorly-controlled diabetic to a new insulin. To the question, "Can the number of insulins be reduced?" the answer is "No," for the present and for a very considerable time to come. The perfect insulin to suit all diabetics has not yet been discovered. There are always some diabetics who are best controlled by a particular insulin or particular combinations of insulins, to whom no others suit as well. These diabetics should be able to obtain their proper insulins. Confusing as it is to have so many insulins, the physician has to accept this situation and to overcome the difficulties by wise choice and intelligent use.

Heinsius, Ernst (Dept. of Ophthalmology of Hospital Heidberg, Hamburg, Germany): DIABETIC RETINITIS IN CHILDHOOD. Deutsche med. Wchnschr. 82:918-19, June 7, 1957.

Ophthalmoscopic examinations of seventy-eight juveniles aged nine to nineteen years in a summer camp for diabetics showed retinal abnormalities in seventeen instances or 22 per cent. Capillary aneurysms or small capillary hemorrhages were found in five children; five had typical white exudates, and eight had venous changes. In addition, absent macular reflexes and depigmentation were observed in five children. All children with diabetic retinitis had had diabetes for at least four years. There was no correlation with the age of the patient or the severity of the disease. Capillary resistance was increased in eight of the seventy-eight patients but in none of the seventeen with retinal abnormalities. Frequent opthalmologic examination is recommended for all diabetic children.

Henneman, Dorothy H.; and Bunker, John P. (Anesthesia Lab., Harvard Med. Sch., Massachusetts Gen. Hosp., Boston, Mass.): THE PATTERN OF INTERMEDIARY CARBOHYDRATE METABOLISM IN CUSHING'S SYNDROME. Am. J. Med. 23:34-45, July 1957.

Under various conditions of glucose loading there is excessive accumulation of lactate and pyruvate in the venous blood of patients with Cushing's syndrome and of subjects receiving 17-hydroxycorticosteroid therapy. The abnormal responses described appear to be peculiar to the states indicated. Although all the facts are not adequately explained, the inference is drawn that the 17-hydroxycorticosteroids inhibit the conversion of pyruvate to acetyl coenzyme A and carbon dioxide, without affecting the tricarboxylic acid cycle directly.

Hennes, Allen R.; Wajchenberg, Bernardo L.; Fajans, Stefan S.; and Conn, Jerome W. (Dept. of Int. Med., University of Michigan Med. Sch., Ann Arbor, Mich.): THE EFFECT OF ADRENAL STEROIDS ON BLOOD LEVELS OF PYRUVIC AND ALPHA-KETOGLUTARIC ACID IN NORMAL SUBJECTS. Metabolism 6:339-45, July 1957.

The authors demonstrate that the blood levels of glucose, pyruvate and alpha-ketoglutarate have been studied in normal subjects during glucose tolerance tests, before and after the administration of 11-17 oxygenated adrenal steroids. These steroids resulted in great loss of carbohydrate tolerance which was associated with a marked increase in levels of pyruvate in the fasting state and with further prompt increases following ingestion of glucose. There was no corresponding increase in the levels of alpha-ketoglutarate. These results suggest that adrenal steroids exert an inhibiting effect on the utilization of pyruvate.

Höpker, W. (Dept. of Medicine of the City Hospital, Luedenscheidt, Germany): MINIMUM INSULIN REQUIREMENT AND SULFONYLUREA TREATMENT IN DIABETES MELLITUS. Klin. Wchnschr. 35:668-72, 1957.

An attempt was made to establish the maximal dose of insulin which could be replaced by oral hypoglycemic sulfonylureas. All newly hospitalized diabetic patients were placed on a standard diet and their minimum insulin requirement under controlled conditions was determined. In many instances this minimal effective dose was significantly below the amount of insulin which the patients had been accustomed to use. After this control period the patients were placed on sulfonylurea medication. In a group of 149 unselected cases it was found that only those patients could be transferred satisfactorily to the oral drug who had a minimum effective daily insulin requirement of not more than 28 to 32 units of a depot-preparation. Patients who had not been on insulin treatment prior to admission received the standard diet and were then placed on the oral drug. If no satisfactory response was obtained, the patients were treated with insulin for ten to fourteen days, and a second trial with the oral drugs was made. A number of patients who had not been responsive at first could be controlled at this second trial. This experience is interpreted as evidence that insulin treatment permitted some functional recovery of the islet system which then enabled the beta cells to respond with increased insulin production to the sulfonylurea stimulus. It is interesting that the author emphasizes the importance of strict adherence to dietary restrictions when the oral drugs are used and reports that several patients voluntarily returned to insulin because of the greater margin of safety it supplies.

Janes, Ralph G.; and Ellis, Philip P. (Dept. of Anat., and Ophth., Coll. of Med., State University of Iowa, Iowa City, Ia.): VASCULAR CHANGES IN EYES OF DIABETIC RATS: ALTERATIONS IN THE ANTERIOR SEGMENT. A.M.A. Arch. Ophth. 57:218-23, February 1957.

The paper describes the gross and histological changes found to occur in the eyes of alloxan-diabetic rats. The rats were followed periodically to observe development of cataract, hyphema and corneal vascularization. Studies of the intraocular vascular system were made by injections of neoprene latex or India ink. It appeared that the iris blood vessels first became engorged and burst. Secondary hyphema and glaucoma interfere with corneal metabolism, permitting ingrowth of new vessels.

Kimmelstiel, Paul (Dept. of Path., Charlotte Memorial Hosp., Charlotte, N. C.): GLOMERULOSCLEROSIS. J. Mt.

Sinai Hosp. 23:657-62, September-October 1956.

The original description of a nodular glomerular lesion was based on morphologic observations, and the correlation of eight such instances with diabetes, hypertension, and nephrosis could be no more than tentative. Reports of similar cases appeared until it finally became clear that the glomerular lesion was very closely, if not invariably, associated with diabetes. Other observations, however, raised serious doubts and the existing confusion was not clarified until Bell pointed out two types of glomerular lesions, the nodular and the diffuse. He showed that nodular sclerosis, as originally described, was indeed specific for diabetes and could be regarded as pathognomonic. Diffuse glomerulosclerosis, however, which only in its end stage may be confused with the end stage of the nodular type, was nonspecific, although it occurs rather frequently in diabetic patients. Much emphasis has lately been put on capillary aneurysms, believed by some to constitute the initial change.

The author does not believe, however, that the histogenesis of these two processes is identical. In the first place, retinal aneurysms are saccular, while glomerular capillary dilatations are fusiform or cylindrical, and it is a matter of choice to refer to them as true aneurysms. Secondly, there is no proof that glomerular aneurysms in the human antecede the formation of spherical nodules. The impression gained from a large number of cases seems to point to the opposite conclusion.

The two types of glomerular involvement seem to reflect a concept of diabetes as a complex metabolic disorder which involves more than just abnormal carbohydrate metabolism resulting from insulin deficiency. It is true that glomerulosclerosis does not develop parallel to age, but specifically depends on the duration of demonstrable disturbances of carbohydrate metabolism. If the lack of insulin, however, were the decisive factor responsible, then vascular-renal changes would be preventable by proper control, and there should be a proportionate relation between the severity of diabetes in terms of insulin requirement and severity of vascular-renal disease.

The concept of diabetes as metabolic disorder characterized by the combination of a specific disturbance of carbohydrate metabolism, i.e., insulin deficiency, and a nonspecific factor of rather vague and yet undefined nature is reflected in the glomerular changes which are of a specific and of a nonspecific type. The latter, together with accelerated arteriosclerosis, may take an independent, progressive course, irrespective of the insulin control. The author suggests that the specific morphologic changes take place in the epithelial layer of the glomerular tufts in contact with mesenchyme in the parietal layer of Bowman's membrane and in the tubular basement membrane.

Kocen, R. S. (London, N. W. 10, England): DIABETES MELLITUS WITH ACUTE POLYNEURITIS. Brit. M. J. 2: 100-01, July 13, 1957.

The author describes a case of acute polyneuritis suggestive of a Guillain-Barré syndrome, occurring in a diabetic.

Kohn, J. (Queen Mary's [Roehampton] Hospital, London, England): A RAPID METHOD OF ESTIMATING BLOOD-GLUCOSE RANGES. Lancet *119*: July 20, 1957.

The author describes his experience with a rapid method of estimating blood sugar ranges, based on the use of Clinistix. The method involved placing a drop of fresh blood from the fingertip or ear lobe on the impregnated tip of Clinistix so as to cover a length of about 0.5 cm. Only fresh blood was used because oxalated or citrated blood is more difficult to wash off. The blood was left on the Clinistix for twenty seconds and was then washed off under a stream of running water for a maximum of five seconds. The subsequent green-blue to dark blue color was immediately compared with a color scale. The matching should be completed within twenty-five seconds from the time the blood has been washed off because the color may later increase in intensity. Various batches of Clinistix were compared for sensitivity and no appreciable differences were found. A definite sign of deterioration is a brownish color of the impregnated tip and such a batch of Clinistix should not be used. Results were obtained in 545 samples of blood, and there was a definite and constant correlation between certain ranges of blood glucose levels and the intensity and shade of color. The sensitivity of Clinistix to glucose in blood under the test conditions seems to be about 0.03-0.04 gm. per 100 ml., which is about twice its sensitivity to glucose in urine. Blood sugar levels below 30-40 mg. per 100 ml. did not produce any color. The first trace of a faint greenish-blue color may be seen at a level which is above 30 mg. per 100 ml. A more intense blue-green color indicated a blood sugar range up to 200 mg. per 100 ml., a deeper blue up to 250 mg. per 100 ml., and a navy blue up to 400 mg. per 100 ml. The results were more accurate in the lower ranges with less intense colors. Levels above 400 mg. per 100 ml. probably produce a maximum intensity of color and are too deep for any gradation to be appreciated. There are two main variables in the test: the timing at all three stages—contact with blood, washing and reading—and

the obvious personal variation in appreciation of color. The procedure is simple and rapid, because it does not require any apparatus or reagents, and can be completed in about a minute. The test indicates the clinically important sugar ranges but does not provide exact figures.

Lancaster, W. M. (Victoria Infirmary, Glasgow, Scotland): A SIMPLE METHOD OF BLOOD-SUGAR ESTIMATION. Brit. M. J. 2:83-85, July 13, 1957.

A simple method of blood sugar estimation was tried in a series of eighty diabetic patients, and the results were compared with those obtained by the true blood sugar method of Nelson. The outfit for this simple method is manufactured by the Ames Company (London) Ltd. The most accurate results were obtained when the blood level lay between 100 and 200 mg. per 100 ml. In higher ranges the results were less precise but often were adequate approximations. The test was of no value in diagnosis of hypoglycemia.

Levison, William (Diabetes Clin., Newark Beth Israel Hosp., Newark, N. J.): MANIFESTATIONS OF LATENT DIABETES DURING PREGNANCY. J. M. Soc. New Jersey 54:229-34, May 1957.

Cases of prediabetes or latent diabetes are described which became manifest during pregnancy, recurred during subsequent pregnancies and finally developed permanent diabetes. The importance of early detection of diabetic tendencies in all cases of pregnancy is stressed. The high fetal morbidity and mortality makes active treatment of the prediabetic mother imperative. Hypercorticalism probably causes the manifestation of diabetes during pregnancy in predisposed individuals.

Magee, Kenneth R.; and Critchley, MacDonald (National Hosp., Queen Square, London, England; Dept. of Neurol., University Hosp., Ann Arbor, Mich.): GOWERS' LOCAL PANATROPHY: ITS RELATION TO CERTAIN TYPES OF INSULIN LIPODYSTROPHY. Neurology 7:307-12, May 1957.

In his textbook of neurology (1886) and in a subsequent paper (1903), Sir William Gowers reported a case of "local panatrophy" occurring in a thirty-three-year-old woman. The patient showed wasting of all subcutaneous tissues "down to the bone" in various areas on the trunk, limb, and face. The wasted areas varied considerably in dimensions, from "the size of a nut to an orange."

This disorder has received very little attention. Oppenheim suggested that it was probably a form of scleroderma, and that it might also in many respects be similar to facial hemiatrophy. In contrast to local panatrophy, lipodystrophy resulting from other causes has received more attention. In particular, the lipodystrophy resulting from injection of insulin in diabetic patients has been described by numerous authors. Localized lipodystrophy has also been reported following injection of substances other than insulin, including grass pollen and pituitrin. Localized atrophy of the subcutaneous fat has also been reported after a jelly-fish sting. Despite the frequency of so-called insulin lipodystrophy following the injection of insulin into a particular area of the body, extremely few cases have been reported where the wasting of subcutaneous tissue occurred at a site far distant from that used for the injection.

The author presents two case reports, one illustrating Gowers' "local panatrophy," and the other illustrating an example of atrophy occurring at a site distant to the site used for injection of insulin in a diabetic. Unfortunately, no biopsy material was available on case one or other reported cases of Gowers' local panatrophy. However, clinically there is no doubt that case one fulfilled the requirements for this diagnosis. Furthermore, the clinical picture in case two was similar to the previous reported cases of atrophy occurring at a site distant from that used for the injection of insulin. The findings on muscle biopsy were quite specific in showing a perivasculitis in muscle and fat. This type of inflammatory reaction is typical of the lesions found in hypersensitivity reactions, and strongly suggests an allergic basis for the production of the subcutaneous atrophy. The factors producing this allergic reaction are unknown, but certainly a sensitivity to the insulin preparation received by the patient seems a distinct possibility. An allergic reaction would seem more plausible than any hypothesis based upon a localized action of insulin.

Malins, John (Birmingham United Hospitals, Birmingham, England): HYPOGLYCAEMIA. M. Press 238:11-14, July 3, 1957.

A review of symptoms and a tabulation of the known and theoretically possible causes of hypoglycemia are presented.

Marble, Alexander (Harvard Med. Sch., Joslin Clin. and New England Deaconess Hosp., Boston, Mass.): LENTE INSULIN IN THE TREATMENT OF DIABETES MELLITUS. M. Clin. North America 485-94, March 1957.

The author discusses in some detail the use of Lente insulin in the treatment of diabetes. It is recommended that Lente insulin be used or considered in new diabetics beginning insulin treatment, or in those patients whose regulation has been unsatisfactory with other insulin, and

also in patients who show any evidence of allergy to other varieties of insulin. The point is brought out that the reaction time of Lente insulin is almost identical with NPH, and that the two can be interchanged without much change in the diabetic condition. Other advantages of Lente insulin include the lack of added protein, thus the possibility of producing fewer allergic responses than other insulins and the theoretical advantage that, because it does contain no protamine, its administration over a long period of time may not exert any effect on the blood lipids which has been postulated that protamine does. The author states that Lente insulin represents a definite advancement in the development of insulin preparations.

Medicine and the Law (Times, June 21): INSULIN COMA IN A DRIVER. Lancet *1345*: June 29, 1957.

The case of a diabetic driver who suffered an insulin reaction is briefly discussed. He was accused of being in charge of a motor vehicle while under the influence of a drug and was found guilty but given an absolute discharge.

Mendelow, Harvey; and Brill, Gerald (Mount Sinai Hosp., New York, N. Y.; National Inst. of Arthritis and Metabolism, U. S. P. H. S., Bethesda, Md.): INTERCAPILLARY GLOMERULOSCLEROSIS: A CLINICO-PATHOLOGIC STUDY. J. Mt. Sinai Hosp. *23*:663-70, September-October 1956.

One hundred and nine post-mortem cases of diabetes mellitus occurring in 1,454 consecutive necropsies, an incidence of 13.3 per cent, were reviewed. The clinical and pathologic features of these cases were studied independently, and an attempt was made then at clinico-pathologic correlation.

Thirty-five cases of intercapillary glomerulosclerosis or 32 per cent were encountered in this group of diabetic patients. The presence of intercapillary glomerulosclerosis does not appear related to age or sex and is not proportional to the clinical severity of the diabetes. However, there is a direct relationship to the duration of the diabetic symptoms, a greater incidence being found in those whose clinical course is of long duration, even among the younger diabetics. From the clinical standpoint, only nine of the thirty-five cases, or 26 per cent, displayed the classical triad of hypertension, albuminuria, and edema. Three patients who had the triad were among the diabetics without the specific pathologic lesions in the kidney.

The Kimmelstiel-Wilson lesion is specific for diabetes mellitus. It is thought to occur as a result of metabolic changes in the basement membrane permitting transudation and accumulation of materials in the intercapillary space or mesangium with progressive glomerular damage and final obliteration.

Mookerjea, Sailen; and Sadhu, D. P. (Dept. of Biochemistry, Nagpur, India, Dept. of Physiol., Bengal Veterinary College, Calcutta, India): THE MECHANISM OF CHOLESTEROL SYNTHESIS IN DIABETES. Metabolism *6*:326-30, July 1957.

The authors demonstrate that free and esterified cholesterol in blood, liver and kidney of rats with alloxan diabetes of two to four weeks' and six to seven weeks' duration demonstrate a rise in cholesterol in the diabetic rats for six to seven weeks. Acetoacetate formation from acetate was considerably accelerated in livers of diabetic animals. Oxidation of acetoacetate and succinate was unaffected in such liver slices, but acetate oxidation was depressed. Kidney slices show a gradually increasing depression of acetate, acetoacetate and succinate oxidation in alloxan diabetes. A possible correlation between increased ketogenesis, decreased acetate and acetoacetate oxidation, and rise of cholesterol has been discussed.

Moorhouse, John A.; and Kark, Robert M. (Dept. of Med., Presbyterian Hosp., Cook County Hosp., University of Illinois Hosp., Chicago, Ill.): FRUCTOSE AND DIABETES. Am. J. Med. *23*:46-58, July 1957.

This paper reviews present interest in fructose as a medium for management in diabetic ketosis and the light thrown by its use upon the nature of the metabolic defects in diabetes and the actions of insulin. Fructose was delivered to the diabetic patients under experiment by continuous tube feeding, insulin having been withdrawn courageously. In the patients with milder diabetes there was improved utilization of carbohydrate, and with this, improved utilization of fat and protein. In the patients with severe diabetes fructose administration was ineffective. Apart from the impracticability of continuous oral feeding, a prerequisite for reasons made clear in the text, the authors conclude that fructose has little therapeutic usefulness. They make deductions as to the site and nature of the metabolic block in diabetes and on the action of insulin.

Mulholland, Henry B.; and Thornton, W. Norman, Jr. (Depts. of Int. Med. and Obst. and Gynecol., University of Virginia Sch. of Med., Charlottesville, Va.): PREGNANCY AND DIABETES. GP *16*:74-77, July 1957.

A review of the problem in the diabetic pregnancy is presented, and reference to the prediabetic state is made. The article covers the question of hazards to the mother and the causes of infant mortality. Meticulous regulation of diabetes, prevention of edema and hydramnios, careful watching for early signs of toxemia and renal disease are suggested.

Hormones are not routinely used.

Murdock, Thomas P. (Meriden, Conn.): THE MODERN HISTORY OF DIABETES MELLITUS—ITS MANAGEMENT. Connecticut M. J. 21:640-42, July 1957.

The diabetic of today presents a unique psychological picture. After the diagnosis is established, and he is told what the general picture is, and what his pattern of life must be, his first question is, "Doctor, will I live?" After another week, he asks for more food than he has been given. Finally, he resists insulin. These changes take place in a matter of days.

It has been the author's experience that practically all diabetics require insulin excepting the very, very mild ones. Almost all will innocently, carelessly or knowingly violate their diets somewhere along the way. These violations, even though the diabetes is mild, will place an added load on the remaining islands of Langerhans. This results in the almost certain requirement of insulin.

Nikkilä, E. A.; and Kerppola, W. (First Med. Clin., University of Helsinki, Helskini, Finland): ACETYLATION IN DIABETES MELLITUS. Scandinav. J. Clin. & Lab. Invest. 9:105-06, 1957.

As a measure of acetylation capacity, the ratio of acetylated to total p-aminobenzoic acid, found in the urine excreted during the three hours after oral administration of 1 gm. of p-aminobenzoic acid, has been measured in thirty-one diabetic and twenty-two normal human subjects. The groups were matched as to age, sex and body build, and the diabetic subjects were subdivided according to the stage and the response to treatment of their disease. The ability to acetylate a foreign amine such as p-aminobenzoic acid is definitely increased during diabetic acidosis and often over normal limits also in insulin-needing diabetics without acidosis. It is normal in cases which are later controlled by oral carbutamide or diet only. In previously untreated cases with acidosis, the acetylation ratio falls somewhat on insulin administration, but often remains high in spite of an apparently perfect control of the diabetic state.

The above findings are in the opposite sense to those observed by others in the alloxan-diabetic rat, and this may indicate a difference between these two diabetic states.

Olson, O. Charles (Spokane, Wash.): TREATMENT OF DIABETES WITH ORAL HYPOGLYCEMIC AGENTS: TRIAL OF CARBUTAMIDE AND TOLBUTAMIDE IN FIFTY CASES. Northwest Med. 57:588-95, May 1957.

A brief review of pharmacologic effectiveness, toxicity, theories of mode of action, and suggested dosage of the oral hypoglycemic agents is presented.

The author had experience with fifty patients who were given one or both of the two agents available to him, namely tolbutamide or carbutamide. Seventeen of the patients were excluded from the follow-up for various reasons, leaving a total of thirty-three. Of these, twenty-seven responded satisfactorily. In an addendum to the article, the author reported that four of the twenty-seven subsequently were not controlled satisfactorily and had to resume insulin therapy. No serious side reactions were reported, although four patients were discontinued because of minor side reactions.

Pennock, L. Lewis (Pittsburgh, Pa.): SULFONYLUREAS IN THE TREATMENT OF DIABETES: OBSERVATIONS IN 100 CASES. Pennsylvania M. J. 60:613-17, May 1957.

Two sulfonylureas (carbutamide and tolbutamide) have been used in the treatment of 100 diabetic patients. Seventy-seven cases were satisfactorily controlled by these drugs and a restricted diet. In fifty-four cases these drugs were successful in completely replacing insulin in treatment. Mild transitory skin rash was seen in two cases and mild nausea in several other cases. These were the only side effects observed.

Ralli, Elaine P.; Barbosa, Xavier; Beck, Edith M.; and Laken, Bertram (Dept. of Med., College of Medicine, New York University-Bellevue Med. Center, New York, N. Y.): SERUM ELECTROPHORETIC PATTERNS IN NORMAL AND DIABETIC SUBJECTS. Metabolism 6:331-38, July 1957.

The authors studied the electrophoretic serum protein patterns in ninety-six diabetic and fifty nondiabetic controls. They were divided into those over and those under forty-five years of age. The patterns in younger control subjects were accepted as normal with a total protein of 7.5, the mean serum albumin of 3.3, the mean alpha globulin of 1.2, the mean beta globulin of 1.2 and the mean gamma globulin of 1.8. The older subjects demonstrated the same total serum proteins. But the albumin was lower, namely 3.0. Alpha and beta globulin levels were the same, but the gamma level was higher, namely 2.0. The young diabetic subjects showed the mean total protein of 7.2, the mean albumin of 3.0, the mean alpha globulin of 1.3, the mean beta globulin of 1.1 and the mean gamma globulin of 1.8. The older diabetic subjects showed changes largely in the beta and gamma globulin fractions, both of them being higher in the older subjects, namely 1.3 and 1.9, respectively. Insulin sensitivity tests in fifteen diabetic patients showed a decreased sensitivity to insulin in the subjects under forty-five which was not related to the electrophoretic protein pattern fractions. There was no consistent relationship between the distribution of the protein fractions and the incidence of retinopathy and albuminuria.

Rifkin, Harold (Montefiore Hosp., New York, N. Y.): THE KIMMELSTIEL-WILSON SYNDROME: CLINICAL ASPECTS. J. Mt. Sinai Hosp. 23:674-82, September-October 1956.

The clinical manifestations and significance of the capillary vascular lesions in diabetes mellitus have been subject of many recent publications. The specificity of the clinical syndrome has been questioned. There is little doubt that a fully developed clinical syndrome characterized by diabetes, edema, hypertension, proteinuria, azotemia and diabetic retinopathy is noted in approximately 10 to 15 per cent of the patients with the specific nodular lesion of the glomerulus. Unfortunately, a number of other situations may give rise to a similar sequence of symptoms and signs. This includes diabetics who have arteriosclerotic heart disease, hypertensive cardiovascular disease or chronic pyelonephritis with superimposed congestive heart failure; or patients, who in addition to their diabetes develop other etiologic bases for a nephrotic syndrome, such as renal amyloidosis, or nephrotic glomerulonephritis, of the rare case of coexisting diabetes mellitus and renal vein thrombosis or diffuse collagen disease.

A most important problem facing the clinician is a determination of the earliest clinical signs of the disease. This is particularly significant, since any future medical or surgical regime may be too late to affect already irreversible lesions. Perhaps, repeated use of the ophthalmoscope may give us valuable information, since it has been repeatedly stated that patients with retinal microaneurysms already have renal involvement morphologically in spite of the absence of any clinical or laboratory findings pointing to glomerular disease.

Perhaps serial renal biopsies may be helpful, since Iverson and his co-workers have shown the presence of so-called diffuse lesions coexisting with diabetic retinopathy, in the absence of the nodular lesion. It is questionable whether pathologists would agree that such diffuse lesions are conceivably the forerunners of the nodular lesion, which the Scandinavian workers as well as some of our own people have recently claimed.

The amelioration of diabetes as the renal lesion progresses, and the rarity of acidosis in the course of the diabetic patient's lifetime, were first pointed out by Zubrod and his associates of The Johns Hopkins Hospital. This has since been challenged by many clinicians. While it is true that many patients with diabetic glomerulosclerosis tend to develop a diminished insulin requirement, similar findings can be observed with a wide variety of other nonspecific renal diseases. The more likely explanation would appear to be a marked diminution of caloric intake, rather than a specific metabolic disturbance. The argument still continues to rage concerning the effects of control of diabetes on the development of renal and retinal lesions. This is difficult to evaluate, since definition of control varies so widely. Granted that a high incidence of severe diabetic retinopathy and nephropathy is associated with poor levels of control, one must still be cognizant of the fact that a fair percentage of patients with good control develop extensive vascular damage. The author has made a correlative study of serum lipids and serum mucopolysaccharides in uncomplicated diabetic patients and such with retinopathy and nephropathy. The serum cholesterol, lipid phosphorus and total lipids were usually elevated in patients with the fully developed Kimmelstiel-Wilson syndrome. In diabetic retinopathy, the serum cholesterol and lipid phosphorus remained within the normal range, but the total lipids were elevated. The significance of these results is as yet unclear. Much evidence from the clinical, experimental, and therapeutic standpoints has been marshalled to indicate that a possible relationship exists between increased pituitary-adrenal cortical activity and the development of the specific vascular lesions. Diabetics with retinopathy and nephropathy have been found to excrete normal amounts of C 19-11 oxysteroids which are primarily derivatives of Compound F. When considered in the light of the impaired renal clearance of these patients, these so-called normal amounts may possibly be considered as excessive.

Robertson, James (King's College Hosp., London, England): THE SICK DIABETIC. M. Press 237:571-73, June 26, 1957.

The changes in diabetic control due to intercurrent illness are usually easy to recognize and temporary in nature. Careful observation must be kept on the patient, and urine tests done regularly for sugar and acetone. Whenever there is any sign of difficulty in control, soluble insulin must be used in adequate quantities. Careful watch for hypoglycemia must be kept in the convalescent phase.

Robillard, Rosario (Montreal, Quebec): PRELUDIN TREATMENT OF OBESITY IN DIABETES MELLITUS: PRELIMINARY REPORT. Canad. M. A. J. 76:938-40, June 1, 1957.

In this study, Preludin was a useful adjunct to the usual weight reduction program in twenty-four obese diabetics. Cessation or reduction in the dosage of insulin parallels directly the degree of weight loss.

Scott, E. M.; and Griffith, Isabelle V. (Arctic Health Res. Center, Pub. Health Ser., Dept. of Health, Education & Welfare, Anchorage, Alaska): DIABETES MEL-

LITUS IN ESKIMOS. Metabolism *6*:320-25, July 1957.

The authors demonstrate that diabetes mellitus is rare among Alaskan Eskimos and in most localities it is completely unknown. Three confirmed and two possible cases in a population of 16,000 are known. The three confirmed cases are all from the area around Nome. Part of the rarity can be described through age, 23 per cent of the population being over thirty-five years of age. However, among Eskimos obesity occurs in 10 per cent of the men and 27 per cent of the women, who weigh at least 30 lbs. more than whites of the same age, sex and height. Eskimos over sixty show little or no tendency to be overweight. It is suggested that the rarity of diabetes, in part, is a racial characteristic.

Skillern, Penn G.; and McCullagh, E. Perry (Cleveland Clin. Foundation, and The Frank E. Bunts Educational Inst., Cleveland, Ohio): HYPERFUNCTION AND HYPOFUNCTION OF ENDOCRINE GLANDS AND DIABETES MELLITUS. J. Indiana M. A. 50:701-09, June 1957.

Diabetes mellitus may be precipitated by hyperfunctioning tumors of the pituitary, adrenal cortex, adrenal medulla, thyroid, and hyperplasia of the adrenal cortex and thyroid. After surgical correction of the pathologic condition, the diabetes may or may not be reversible. Instances of reversible diabetes with acromegaly due to spontaneous causes, cobalt treatment, and estrogen therapy are described. One patient with Cushing's syndrome and pituitary tumor had a temporary remission of the diabetes after cobalt eradication of the pituitary. The diabetes mellitus of one patient with pheochromocytoma who was admitted in diabetic acidosis, disappeared after removal of the pheochromocytoma. The occurrence of diabetes mellitus in two patients with aldosteronism due to adrenal tumor suggests that a hormone may be secreted which has some corticoid action. A diabetic glucose tolerance curve in a patient with hyperthyroidism may or may not be due to diabetes mellitus. An elevated fasting blood sugar in the presence of hyperthyroidism is due to diabetes mellitus.

Smout, M. S.; and Watson, E. M. (Univ. of Western Ontario; and Victoria Hospital, London, Ontario, Canada): COMPARISON OF A RAPID BLOOD SUGAR TEST (DEXTROTEST) WITH STANDARD METHODS. Canad. M. A. J. 76:1064-65, June 15, 1957.

After comparing the results obtained through the rapid bedside method (Dextrotest) with the standard laboratory methods, the authors conclude that the rapid procedure may be useful in emergency situations. Gross hyperglycemia can be recognized, but the method does not recognize hypoglycemia directly. They conclude that the procedure is impracticable as a guide for therapeutic control of diabetic patients.

Spirtos, B. N.; and Halmi, N. S. (Dept. of Anat., State University of Iowa, Iowa City, Ia.): INFLUENCE OF SOMATOTROPHIN AND CORTISONE ON THE INSULIN SENSITIVITY OF RATS. Endocrinology 58:193-205, February 1956.

This paper deals with the effects of STH and cortisone singly and together on the insulin sensitivity of intact rats and hypophysectomized, adrenalectomized and hypophysectomized-adrenalectomized rats. Neither showed a significant effect on the fasting blood sugar of the intact rat, though this was not the case when used in combination. Similar results occurred with only the combination treated rats showing decreased insulin sensitivity. Hypophysectomized rats, showing marked insulin sensitivity, were less sensitive when given somatotrophin and more insensitive on cortisone, which increased the fasting blood sugar levels. In the hypophysectomized state the hyperglycemic effect of cortisone was counteracted by appropriate doses of somatotrophin, whereas enhanced insulin resistance was presented when both somatotrophin and cortisone were given. In the adrenalectomized rat, only cortisone was found to be effective in restoring the fasting blood sugar and the insulin sensitivity to normal. Somatotrophin protected hypophysectomized-adrenalectomized rats against the hypoglycemic effects of insulin, without affecting the fasting hypoglycemia.

Stambul, Joseph; and Meranze, David R. (Albert Einstein Med. Center, Philadelphia, Pa.): ATHEROSCLEROSIS IN DIABETES: INTERPRETATION OF THE MECHANISMS OF DIABETES AND THEIR RELATIONSHIP TO ATHEROSCLEROSIS. J. Albert Einstein M. Center 5:74-107, March 1957.

In permanent diabetes (pancreatic and meta) are indicated regulated diabetic diet (low fat, high carbohydrate, moderate caloric value), insulin in proper doses, and the use of lipotropic agents. Atherosclerosis is the end result of a chain of events taking place in the body. Whenever any of those factors preceding the development of atherosclerosis is recognized, corrective measures should be taken in order to prevent further complications.

Wedgwood, J. (Addenbrooke's Hosp., Cambridge, England): DIABETES MELLITUS WITH ACUTE POLYNEURITIS. Brit. M. J. *1*:1346, June 8, 1957.

The author reports a case of true symmetrical polyneuritis occurring in a diabetic. Such a condition has only rarely been noted.

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Analysis of a Survey Concerning Employment of Diabetics in Some Major Industries

An enlightened attitude on the employment of diabetics exists to an encouraging extent in the country's leading business and industrial concerns, judging by an analysis of the results of a survey recently conducted by the Committee on Employment.

A corollary of this conclusion: the larger the company, the more enlightened its attitude. Research apparently confirmed what could have been surmised, for the larger companies have more adequate medical and personnel facilities and set the pace generally in employment practices.

The survey indicates that most of the companies tabulated, the smaller and the larger ones, employ known diabetics; and that most of the companies which do not employ known diabetics do continue in their employ those workers who develop the condition after they are hired.

But the general picture that emerges from an analysis of the survey results is not completely favorable. Some concerns, even the larger ones, do not employ known diabetics; and most concerns, including the larger ones, do not make any concessions as to rotation of shifts for the known diabetics they employ.

These general impressions, however, should be considered against the backdrop of the total results; and the total results, in turn, should be viewed in the light of the extent of the survey and the manner in which it was conducted. It may therefore be appropriate to indicate at the outset the pertinent facts about the survey.

Questionnaires were mailed to 434 business and industrial concerns throughout the country. These companies include virtually all of the largest in the United States.

Each questionnaire was transmitted by a short letter, signed by Dr. Joseph T. Beardwood, Jr., Committee Chairman, which stated:

"The Committee on Employment of the American Diabetes Association is making a survey of important industries in an effort to evaluate their present experience in the employment of diabetics.

"It is important to obtain adequate statistics to proceed further in our work. Our Committee would appreciate your filling out the enclosed questionnaire. . . ."

There was no follow-up to this letter. The question-

naire, while it was kept as simple as possible by the Committee, did require time and effort to complete. Despite these factors, 127 companies completed and returned their questionnaires.

These 127 concerns are a fair sampling of the complete list. They employ approximately 1,900,000 workers.

The Committee divided these 127 companies into the following twenty-one categories, with the number of employees shown for each:

Chemical—299,477; steel—24,381; automotive—424,510; electrical manufacturing—294,650; railroad—68,800; foundry—45,100; paint—375; aircraft manufacturing—149,000; atomic energy—12,000; communication—117,428.

Clinics (serving industry)—33,637; research—3,500; publishing (generally printing and binding)—10,800; clothing manufacturing—12,500; food, liquor and drug—26,600; rubber—118,000; petroleum—106,691; utility—26,750; insurance—54,309; small tool—15,132, and glass container—30,000.

Chart A is a tabulation of the answers to the eight-part questionnaire; it gives the totals of "yes" and "no" answers, as well as the numbers that did not give any answer. These figures are of significance to the Committee, for they provide the basis for determining the nature and direction of its work in the future.

While 123 companies (97 per cent) perform preplacement physical examinations, only 106 companies (83 per cent) include a routine urine examination.

Eighty-eight companies (69 per cent) of the total of 127 employ known diabetics, while thirty-one (25 per cent) do not; eight (6 per cent) did not answer.

Of the thirty-one companies which do not employ known diabetics, seventeen based their policy on "previous poor experience"; sixteen, on "insurance reasons"; four, on "statistics indicating unreliability"; and five, on "other reasons." Eleven gave more than one reason, as the totals indicate.

Companies employing known diabetics rated their "experience as to reliability and absenteeism" as follows: "satisfactory"—sixty-five companies (51 per cent); "same as average worker"—sixty companies (47 per cent); and "unsatisfactory"—seven (6 per cent). Of these companies, forty-four gave more than one answer.

A total of 110 companies (87 per cent) indicated that their employees participated in insurance and other employee benefits. While none of the companies answered in the negative, seventeen did not answer.

Only thirty-five companies (28 per cent) make any concessions as to rotation of shifts for the known dia-

CHART A
Grand Total

Questions:		Total	Per cent
1. Type of business		127	
2. Number of employees		1,871,640	
3. Do you do routine preplacement physical examinations?	Yes:	123	97
	No:	3	2
	Did not answer:	1	1
4. Does this include a routine urine examination?	Yes:	106	83
	No:	21	17
5. Do you employ known diabetics?	Yes:	88	69
	No:	31	25
	Did not answer:	8	6
A. If not, is it based on:			
(1) Previous poor experience?		17	13
(2) Insurance reasons?		16	13
(3) Statistics indicating unreliability?		4	3
(4) Other reasons?		5	4
Note: Eleven (11) gave more than one answer		11	9
B. If you do, what is your experience as to reliability and absenteeism:			
(1) Satisfactory?		65	51
(2) Unsatisfactory?		7	6
(3) Same as average worker?		60	47
Note: Forty-four (44) gave more than one answer		44	35
(4) Do your diabetic employees participate in insurance and other employee benefits?	Yes:	110	87
	No:	0	0
	Did not answer:	17	13
(5) Do you make any concessions as to rotation of shifts?	Yes:	35	28
	No:	68	53
	Did not answer:	24	19
(6) Do you do blood sugars and urines at regular intervals?	Yes:	52	41
	No:	47	37
	Did not answer:	28	22
C. Can you give any statistics on the number of diabetics you employ and any data which would aid the Committee in evaluating the employment of diabetics?		2,658	
6. If you do not employ known diabetics, do you continue in your employ those who develop diabetes after they began working for you?	Yes:	72	56
	No:	1	1
	Did not answer:	54	43
7. If you do retain them, is an employee allowed to continue in the same job if it is one which does not entail danger to others by his acts?	Yes:	107	84
	No:	4	3
	Did not answer:	16	13
8. Does your Medical Department do routine laboratory examinations for your employed diabetics?	Yes:	65	51
	No:	49	39
	Did not answer:	13	10

betics they employ, while sixty-eight (53 per cent) make none; twenty-four (19 per cent) did not answer.

Blood sugars and urinalysis are taken at regular intervals at fifty-two companies (41 per cent), and are not taken at forty-seven (37 per cent); twenty-eight (22 per cent) did not answer.

Though eighty-eight companies said that they employ known diabetics, only sixty-six reported the number of diabetics they employ: a total of 2,658. As the total employees of these 66 companies is 458,366, the diabetics represent 0.58 per cent—a little under the average for diabetics in the general population which is estimated at 0.75 per cent.

Seventy-two companies (56 per cent) stated that, while they do not employ known diabetics, they do continue in their employ workers who develop the condition after they are hired. Only one company replied to the contrary, but fifty-four (43 per cent) did not answer.

Companies which do retain diabetics in their employ were asked if they allow an employee to continue in the same job if it is one which does not entail danger to others by his acts. Replies: yes—107 (84 per cent); and no—four (3 per cent). The remainder, sixteen (13 per cent), did not answer.

A total of sixty-five companies (51 per cent) reported that their Medical Departments do routine laboratory examinations for their employed diabetics; forty-nine (39 per cent) said they do not; and thirteen (10 per cent) did not answer.

The Committee was particularly interested to discover whatever differences might exist in the practices of small and large companies as they affect the employment of diabetics.

For this purpose, it set the figure of 3,000 employees as the dividing line between small and large companies; and tabulated the results of the survey on the basis of this determination. Chart B shows this tabulation.

The major conclusion that can be drawn from these figures was stated at the outset: Large companies have a more enlightened approach to the subject. The answers to two questions bear out this conclusion.

Of the forty-five small (under 3,000 employees) companies, thirty (67 per cent) indicated that they employ known diabetics, while fourteen (31 per cent) said they do not. Of the eighty-two large companies, however, fifty-eight (71 per cent) answered affirmatively; while only seventeen (21 per cent) answered in the negative.

Of the forty-five small companies, thirty-two (71 per cent) reported that they allow an employee who develops diabetes while in their employ to continue at the same job if it is one which does not entail danger to others by his acts; four (9 per cent) said that they did not. Of the large companies, however, seventy-five (91

CHART B
Small and Big Business

Questions:		Small	Large
1. Type of business		45	82
2. Number of employees		77,800	1,793,840
3. Do you do routine preplacement physical examinations?	Yes:	41	80
	No:	1	2
	Did not answer:	3	0
4. Does this include a routine urine examination?	Yes:	38	68
	No:	7	14
5. Do you employ known diabetics?	Yes:	30	58
	No:	14	17
	Did not answer:	1	7
A. If not, is it based on:			
(1) Previous poor experience?		8	9
(2) Insurance reasons?		6	10
(3) Statistics indicating unreliability?		1	3
(4) Other reasons?		0	5
Note: Eleven (11) gave more than one reason.		1	10
B. If you do, what is your experience as to reliability and absenteeism:			
(1) Satisfactory?		21	44
(2) Unsatisfactory?		1	6
(3) Same as average worker?		24	36
Note: Answered more than one part		16	28
(4) Do your diabetic employees participate in insurance and other employee benefits?	Yes:	36	74
	No:	0	0
	Did not answer:	9	8
(5) Do you make any concessions as to rotation of shifts?	Yes:	5	30
	No:	29	39
	Did not answer:	11	13
(6) Do you do blood sugars and urines at regular intervals?	Yes:	13	39
	No:	19	28
	Did not answer:	13	15
C. Can you give any statistics on the number of diabetics you employ and any data which would aid the Committee in evaluating the employment of diabetics?		343	2,315
6. If you do not employ known diabetics, do you continue in your employ those who develop diabetes after they began working for you?	Yes:	26	46
	No:	0	1
	Did not answer:	19	35
7. If you do retain them, is an employee allowed to continue in the same job if it is one which does not entail danger to others by his acts?	Yes:	32	75
	No:	4	0
	Did not answer:	9	7
8. Does your Medical Department do routine laboratory examinations for your employed diabetics?	Yes:	17	26
	No:	21	28
	Did not answer:	7	28

per cent) answered affirmatively and none answered in the negative. In addition, there were more small companies than large ones which did not answer.

The conclusion supported by these results is understandable. The larger companies have more adequate medical and personnel facilities; and because they are among the country's major industrial concerns, they are the leaders and pace-setters in the current trend toward enlightened employment practices in general.

The Committee was also interested to discern the differences, if any, in the practices governing the employment of diabetics by companies in various sections of the country. It therefore prepared a tabulation of the results of the survey, shown in Chart C, which is based upon a division of the country into these geographical areas: East, West, Midwest and South.

CHART C
Geographical Breakdown

Questions:		East	West	Midwest	South
1. Type of business		45	13	63	6
2. Number of employees		738,638	205,666	873,836	53,500
3. Do you do routine preplacement physical examinations?	Yes:	45	12	59	6
	No:	0	1	2	0
	Did not answer:	0	0	2	0
4. Does this include a routine urine examination?	Yes:	36	11	53	6
	No:	9	2	10	0
5. Do you employ known diabetics?	Yes:	36	10	39	3
	No:	9	3	17	2
	Did not answer:	0	0	7	1
A. If not, is it based on:					
(1) Previous poor experience?		3	1	11	2
(2) Insurance reasons?		3	2	10	1
(3) Statistics indicating unreliability?		0	0	4	0
(4) Other reasons?		5	0	0	0
B. If you do, what is your experience as to reliability and absenteeism:					
(1) Satisfactory?		26	8	28	3
(2) Unsatisfactory?		3	0	4	0
(3) Same as average worker?		24	4	30	2
(4) Do your diabetic employees participate in insurance and other employee benefits?	Yes:	40	13	53	5
	No:	0	0	0	0
	Did not answer:	5	0	10	1
(5) Do you make any concessions as to rotation of shifts?	Yes:	15	5	13	2
	No:	21	6	37	4
	Did not answer:	9	2	13	0
(6) Do you do blood sugars and urines at regular intervals?	Yes:	23	6	22	1
	No:	13	5	26	3
	Did not answer:	9	2	15	2
C. Can you give any statistics on the number of diabetics you employ and any data which would aid the Committee in evaluating the employment of diabetics?		737	860	972	89
6. If you do not employ known diabetics, do you continue in your employ those who develop diabetes after they began working for you?	Yes:	25	5	39	3
	No:	0	0	0	1
	Did not answer:	20	8	24	2
7. If you do retain them, is an employee allowed to continue in the same job if it is one which does not entail danger to others by his acts?	Yes:	37	10	54	4
	No:	0	1	2	1
	Did not answer:	8	2	7	1
8. Does your Medical Department do routine laboratory examinations for your employed diabetics?	Yes:	26	9	28	2
	No:	16	1	29	2
	Did not answer:	3	3	6	2

These figures suggest no consistent pattern. They do offer some indication that the South is the least interested in the problems of the diabetic employee, but such a deduction should not be considered conclusive because of the relatively few Southern concerns tabulated.

Only six companies in the South, representing 53,500 workers, answered the questionnaire, whereas replies were received from thirteen companies in the West, with a total of 205,666 workers; forty-five companies in the East, with 738,638 workers; and sixty-three companies in the Midwest, with 873,836 workers.

The small number of replies from the South may not constitute a representative sampling of companies in that area. This possibility cautions against reliance on

any conclusions that may be drawn. It also may account for the lack of a consistent pattern in the tabulation.

A tabulation of results by industry was also made by the Committee; while too detailed for inclusion here because of limitations of space, it is available to members of the American Diabetes Association upon request.

The figures indicate that, while 69 per cent of the companies in all categories employ known diabetics and only 25 per cent do not employ them, certain industries show a greater than average reluctance.

For example: railroads (with 68,800 workers)—five out of five said they do not employ known diabetics; food, liquor and drug (26,000)—two out of six; petroleum (106,691)—four out of ten; rubber (118,000)—two out of four; and utilities (26,750)—three out of five.

Rubber and food, liquor and drug were also among the industries which are less inclined to continue a newly detected diabetic in his old job if it does not entail danger to others by his acts. The other industries were aircraft manufacturing (149,000 workers) and clothing manufacturing (12,500).

Only four out of six food, liquor and drug concerns said that they do continue such diabetics in their old jobs; and only two out of four companies in the other three categories answered affirmatively. These four categories were markedly lower than the general industrial average of 84 per cent of affirmative replies.

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Harold Brandaleone, Eugene R. Chapin, *by invitation,* Warren F. Draper, *by invitation,* Verne K. Harvey, *by invitation,* George A. Jacoby, *by invitation,* Harvey C. Knowles, Jr., Eldon S. Miller, Robert M. Packer, Jr., Lester J. Palmer, Maurice Protas, Thomas P. Sharkey, Nelson M. Taylor, Edward Tolstoi, C. Richard Walmer, *by invitation;* in addition, Chairmen of Committees on Employment of Affiliate Associations will serve *by invitation.*

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SCIENTIFIC EXHIBITS

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George E. Anderson, John E. Howard, Robert L. Jackson, William R. Kirtley, Arnold Lazarow, Thomas H. McGavack, Henry B. Mulholland, Leon S. Smelo, Robert H. Williams

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INFORMATIONAL COMMITTEE ON ORAL HYPOGLYCEMIC COMPOUNDS

Arthur R. Colwell, Sr., Chairman
Dwight J. Ingle, Maurice E. Krahl, Rachmiel Levine, Henry T. Ricketts

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DELEGATES TO NATIONAL HEALTH COUNCIL

Alexander Marble, Herbert Pollack, J. Richard Connelly

EIGHTEENTH ANNUAL MEETING

As previously announced, the Eighteenth Annual Meeting of the American Diabetes Association will be held at the Hotel Mark Hopkins in San Francisco, June 21-22, 1958, immediately prior to the Annual Session of the American Medical Association, June 23-27. Information about hotel reservations will be sent to members shortly.

SCIENTIFIC PROGRAM

Physicians and other scientists, who would like to present papers at the Scientific Sessions, are invited to sub-

mit abstracts to Francis D. W. Lukens, M.D., Chairman of the Committee on Scientific Programs. Eleven copies of the abstracts, which are requested in order to expedite review by the Committee, should be sent to Dr. Lukens in care of the national office.

1958 LILLY AWARD

Jan. 1, 1958, is the deadline for nominations for the second annual Lilly Award, which is supported by Eli Lilly and Company and consists of $1,000 and a medal. The Award will be given at the Eighteenth Annual Meeting of the American Diabetes Association in San Francisco, June 21-22, 1958. The following stipulations govern the contest.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before January 1 of the year of the award. The nomination should be accompanied by full information concerning the nominee's personality, training and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominee's publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. At the discretion of the Committee on Scientific Awards, the award may be given for work published during the year prior to January 1 of the same year of the award. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on the subject of his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and the medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

1957-58 MEDICAL STUDENT-INTERN ESSAY CONTEST

Medical students, interns and physicians within two years after their graduation from medical school are invited to enter the sixth Medical Student-Intern Essay Contest sponsored by the American Diabetes Association. Any subject relating to diabetes and basic metabolic problems may be selected.

The author or authors of the best paper reporting original work, whether laboratory investigation or clinical observation, will receive an award of $250. This prize is again made possible through the kindness of the St. Louis Diabetes Association.

The author or authors of the best review article or case report will be awarded a prize of $50.

Papers will be judged on the basis of value of the material and method of presentation.

Members of the American Diabetes Association and subscribers to DIABETES are requested to encourage medical students and interns to enter the contest. Entrants should submit the original and two copies of their manuscript. The manuscript should be typewritten and double-spaced, and mailed by April 1, 1958, to: Committee on Scientific Awards, American Diabetes Association, Inc., 1 East 45th St., New York 17, N.Y.

IDF HOLDS THIRD CONGRESS

Members of the American Diabetes Association and its Affiliates may be able to fly by chartered plane at reduced rates to attend the next Congress of the International Diabetes Federation at Düsseldorf, Germany. Requests for passage on chartered plane must be received before Jan. 1, 1958. The Congress will be held July 21-25, 1958.

Howard F. Root, M.D., Vice President of IDF, requests those interested to address inquiries and reservations to the Manning Travel Bureau, Hotel Kenmore, Commonwealth Avenue, Boston, Massachusetts. Additional information will be sent to members of the American Diabetes Association in the near future.

NEW MEMBERS

ACTIVE

The following were elected as of Nov. 1, 1957:

California
Cherniss, Edward I. — Fresno

Colorado
Dines, David E. — Denver

Connecticut
Gloetzner, Henry J. — Norwalk

Illinois
McMillan, J. Charles, Jr. — Oak Park

Indiana
Peck, Franklin B., Jr. — Indianapolis

Michigan
Ackerman, Irving P. — Ann Arbor

Minnesota
Griffiths, Edward K. — Rochester
Messer, James Walter — Rochester

Missouri
Gilkey, Harry M. — Kansas City
Lacy, Paul E. — St. Louis
Rosecan, Marvin — Olivette

New Jersey
Gross, Milton — Jersey City
Rogers, James A. — Paterson

New York
Davies, Fel G. — Utica

Ohio
Oseasohn, Robert O. — Cleveland Heights

Pennsylvania
Hausberger, Franz X. — Philadelphia
Myers, Charles E. — Kingston
Soxman, Don G. — Connellsville
Trueman, Robert H. — Philadelphia
Wiener, Leon J. — Philadelphia

Texas
Dobson, Harold L. — Houston

U. S. Possessions

Puerto Rico
de la Noceda, Hilda Garcia — Rio Piedras

Other Countries

Canada
Clamen, Marvin — Montreal, Quebec
Little, James Alexander — Toronto, Ontario

Denmark
*Hallas-Moller, Knud — Copenhagen
Schambye, Per — Copenhagen

East Germany
Katsch, Gerhardt — Greifswald

*Transfer from Associate to Active Membership

NEWS NOTES

PERSONALS

WILFRED DAVID, M.D., has been assigned to the Chronic Disease Program, as Chief of the Program Services, in the Department of Health, Education, and Welfare in Washington, D.C. As such he will be responsible for the Diabetes Program.

W. STANLEY HARTROFT, M.D., St. Louis, participated in a five-day conference held by the World Health Organization to study the classification of atherosclerotic lesions and to make recommendations for a unified nomenclature of the terms used in various parts of the world. Fifteen outstanding scientists from five continents attended the meeting, which began October 7 in Washington.

HENRY B. MULHOLLAND, M.D., Charlottesville, Virginia, and ROBERT H. WILLIAMS, M.D., Seattle, Washington, have accepted membership on the National Advisory Arthritis and Metabolic Diseases Council for the term 1957-61. Their appointments have just been announced by the Public Health Service, U.S. Department of Health, Education, and Welfare.

RICHARD P. STETSON, M.D., Boston, has been appointed to the Veterans Administration Special Medical Advisory Group. Dr. Stetson was one of the four new members recently appointed to this group, which meets quarterly to advise the Chief Medical Director on professional problems.

OBITUARY

BERNARD RABINOVITZ, M.D., Springfield, Massachusetts, died Feb. 13, 1957. Born in Russia June 30, 1880, he received his medical degree from Tufts College of Medicine in 1913. He was Metabolist at the Springfield Hospital from 1934 to 1945, and Consultant from 1945 to 1957. His academic appointments included: Physiatric Institute, Morristown, New Jersey, 1928; Assistant in Metabolism, Postgraduate Hospital, New York City, 1929; and Vice President, Medical Staff, Springfield Hospital, 1956-57. Dr. Rabinovitz organized the Diabetic Clinic at Springfield Hospital in 1932, and actively directed it until 1945. He had been a member of the American Diabetes Association since 1941.